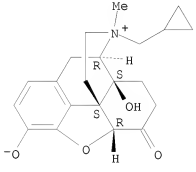
```
=> s methylnaltrexone
L1          34 METHYLNALTREXONE

=> d l1 1-34

L1   ANSWER 1 OF 34  REGISTRY  COPYRIGHT 2008 ACS on STN
RN   1013912-21-4  REGISTRY
ED   Entered STN:  13 Apr 2008
CN   Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-
     oxo-, inner salt, hydrate (1:3), (5α)-  (CA INDEX NAME)
OTHER NAMES:
CN   N-Methylnaltrexone betaine trihydrate
FS   STEREOSEARCH
MF   C21 H25 N O4 . 3 H2 O
SR   CA
LC   STN Files:   CA, CAPLUS
CRN  (1013911-70-0)

Absolute stereochemistry.
```



●3 H_2O

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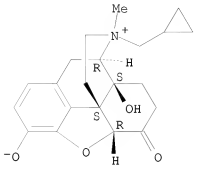
                1 REFERENCES IN FILE CA (1907 TO DATE)
                1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1   ANSWER 2 OF 34  REGISTRY  COPYRIGHT 2008 ACS on STN
RN   1013912-18-9  REGISTRY
ED   Entered STN:  13 Apr 2008
CN   Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-
     oxo-, inner salt, hydrate (1:2), (5α)-  (CA INDEX NAME)
OTHER NAMES:
CN   N-Methylnaltrexone betaine dihydrate
FS   STEREOSEARCH
MF   C21 H25 N O4 . 2 H2 O
SR   CA
LC   STN Files:   CA, CAPLUS
CRN  (1013911-70-0)
```

Absolute stereochemistry.



● 2 H_2O

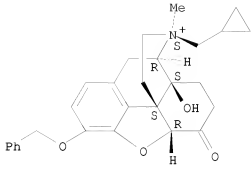
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 3 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1013912-16-7 REGISTRY
ED Entered STN: 13 Apr 2008
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-14-hydroxy-17-methyl-6-oxo-3-(phenylmethoxy)-, (5α,17S)-, methyl sulfate (1:1) (CA INDEX NAME)
OTHER NAMES:
CN (S)-O-Benzyl-N-methylnaltrexone methyl sulfate
FS STEREOSEARCH
MF C28 H32 N O4 . C H3 O4 S
SR CA
LC STN Files: CA, CAPLUS

CM 1

CRN 1013912-15-6
CMF C28 H32 N O4

Absolute stereochemistry.



CM 2

CRN 21228-90-0
CMF C H3 O4 S

Me—O—SO_3^-

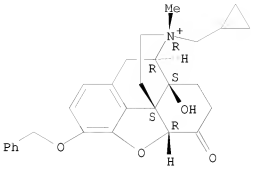
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 4 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1013912-11-2 REGISTRY
ED Entered STN: 13 Apr 2008
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-14-hydroxy-17-methyl-6-oxo-3-(phenylmethoxy)-, (5α,17R)-, methyl sulfate (1:1) (CA INDEX NAME)
OTHER NAMES:
CN (R)-O-Benzyl-N-methylnaltrexone methyl sulfate
FS STEREOSEARCH
MF C28 H32 N O4 . C H3 O4 S
SR CA
LC STN Files: CA, CAPLUS

CM 1

CRN 1013912-10-1
CMF C28 H32 N O4

Absolute stereochemistry.



CM 2

CRN 21228-90-0
CMF C H3 O4 S

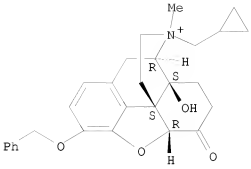
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 5 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1013912-07-6 REGISTRY
ED Entered STN: 13 Apr 2008
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-14-hydroxy-17-methyl-6-oxo-3-(phenylmethoxy)-, (5α)-, methyl sulfate (1:1) (CA INDEX NAME)
OTHER NAMES:
CN O-Benzyl-N-methylnaltrexone methyl sulfate
FS STEREOSEARCH
MF C28 H32 N O4 . C H3 O4 S
SR CA
LC STN Files: CA, CAPLUS, CASREACT

CM 1

CRN 1013912-06-5
CMF C28 H32 N O4

Absolute stereochemistry.



CM 2

CRN 21228-90-0
CMF C H3 O4 S

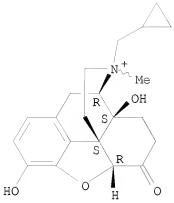
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 6 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1013912-02-1 REGISTRY
ED Entered STN: 13 Apr 2008
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, (5α)-, methyl sulfate (1:1) (CA INDEX NAME)
OTHER NAMES:
CN N-Methylnaltrexone methyl sulfate
FS STEREOSEARCH
MF C21 H26 N O4 . C H3 O4 S
SR CA
LC STN Files: CA, CAPLUS, CASREACT

CM 1

CRN 83387-25-1
CMF C21 H26 N O4

Absolute stereochemistry.



CM 2

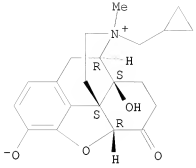
CRN 21228-90-0
CMF C H3 O4 S

Me—O—SO3-

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 7 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1013911-96-0 REGISTRY
ED Entered STN: 13 Apr 2008
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, inner salt, hydrate (2:1), (5α)- (CA INDEX NAME)
OTHER NAMES:
CN N-Methylnaltrexone betaine hemihydrate
FS STEREOSEARCH
MF C21 H25 N O4 . 1/2 H2 O
SR CA
LC STN Files: CA, CAPLUS
CRN (1013911-70-0)

Absolute stereochemistry.

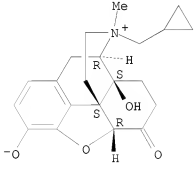


●1/2 H_2O

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 8 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1013911-89-1 REGISTRY
ED Entered STN: 13 Apr 2008
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, inner salt, hydrate (1:1), (5α)- (CA INDEX NAME)
OTHER NAMES:
CN N-Methylnaltrexone betaine hydrate
FS STEREOSEARCH
MF C21 H25 N O4 . H2 O
SR CA
LC STN Files: CA, CAPLUS
CRN (1013911-70-0)

Absolute stereochemistry.

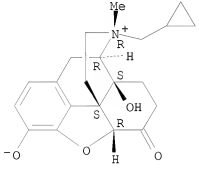


● H_2O

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 9 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1013911-84-6 REGISTRY
ED Entered STN: 13 Apr 2008
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, inner salt, hydrate (1:2), (5α,17R)- (CA INDEX NAME)
OTHER NAMES:
CN (R)-N-Methylnaltrexone betaine dihydrate
FS STEREOSEARCH
MF C21 H25 N O4 . 2 H2 O
SR CA
LC STN Files: CA, CAPLUS
CRN (1013911-74-4)

Absolute stereochemistry.

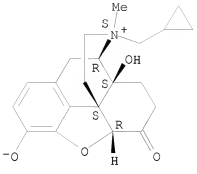


●2 H_2O

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 10 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1013911-79-9 REGISTRY
ED Entered STN: 13 Apr 2008
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, inner salt, (5α,17S)- (CA INDEX NAME)
OTHER NAMES:
CN (S)-N-Methylnaltrexone betaine
FS STEREOSEARCH
MF C21 H25 N O4
SR CA
LC STN Files: CA, CAPLUS

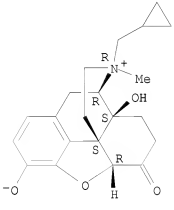
Absolute stereochemistry.



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 11 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1013911-74-4 REGISTRY
ED Entered STN: 13 Apr 2008
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, inner salt, (5α,17R)- (CA INDEX NAME)
OTHER NAMES:
CN (R)-N-Methylnaltrexone betaine
FS STEREOSEARCH
MF C21 H25 N O4
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

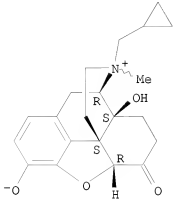


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 12 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 1013911-70-0 REGISTRY
ED Entered STN: 13 Apr 2008
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, inner salt, (5α)- (CA INDEX NAME)

OTHER NAMES:
CN N-Methylnaltrexone betaine
FS STEREOSEARCH
MF C21 H25 N O4
CI COM
SR CA
LC STN Files: CA, CAPLUS, CASREACT

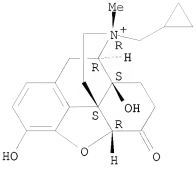
Absolute stereochemistry.



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 13 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 916055-92-0 REGISTRY
ED Entered STN: 20 Dec 2006
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, bromide, (5α,17R)- (CA INDEX NAME)
OTHER NAMES:
CN (17R)-N-Methylnaltrexone bromide
FS STEREOSEARCH
MF C21 H26 N O4 . Br
SR CA
LC STN Files: CA, CAPLUS, CASREACT, USPATFULL
CRN (916055-93-1)

Absolute stereochemistry.

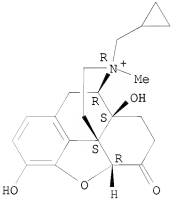


● Br^-

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 14 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 916055-91-9 REGISTRY
ED Entered STN: 20 Dec 2006
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, iodide, (5α,17R)- (CA INDEX NAME)
OTHER NAMES:
CN (17R)-N-Methylnaltrexone iodide
FS STEREOSEARCH
MF C21 H26 N O4 . I
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (916055-93-1)

Absolute stereochemistry.

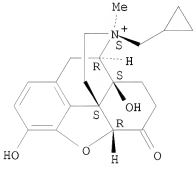


● I^-

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 15 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 916045-21-1 REGISTRY
ED Entered STN: 20 Dec 2006
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,9-dihydroxy-17-methyl-6-oxo-, bromide (1:1), (17S)- (CA INDEX NAME)
OTHER NAMES:
CN (17S)-N-Methylnaltrexone bromide
FS STEREOSEARCH
MF C21 H26 N O4 . Br
SR CA
LC STN Files: CA, CAPLUS, CASREACT, PROUSDDR, TOXCENTER, USPATFULL
CRN (916045-22-2)

Absolute stereochemistry.

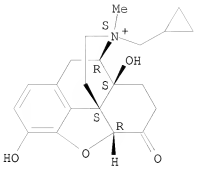


● Br^-

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 16 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 916045-19-7 REGISTRY
ED Entered STN: 20 Dec 2006
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,9-dihydroxy-17-methyl-6-oxo-, iodide (1:1), (17S)- (CA INDEX NAME)
OTHER NAMES:
CN (17S)-N-Methylnaltrexone iodide
FS STEREOSEARCH
MF C21 H26 N O4 . I
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (916045-22-2)

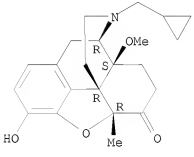
Absolute stereochemistry.



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 17 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 159022-22-7 REGISTRY
ED Entered STN: 17 Nov 1994
CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3-hydroxy-14-methoxy-5-methyl-, (5α)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5β,14-Di-O-methylnaltrexone
FS STEREOSEARCH
MF C22 H27 N O4
SR CA
LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL

Absolute stereochemistry.

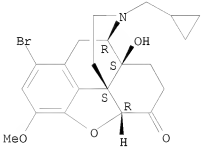


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 18 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 153037-02-6 REGISTRY
ED Entered STN: 16 Feb 1994
CN Morphinan-6-one, 1-bromo-17-(cyclopropylmethyl)-4,5-epoxy-14-hydroxy-3-methoxy-, (5α)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1-Bromo-3-O-methylnaltrexone
FS STEREOSEARCH
MF C21 H24 Br N O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

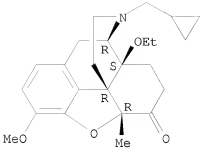


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 19 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 147847-16-3 REGISTRY
ED Entered STN: 28 May 1993
CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-14-ethoxy-3-methoxy-5-methyl-, (5α)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 14-O-Ethyl-O,5-dimethylnaltrexone
CN N-(Cyclopropylmethyl)-14-ethoxy-5-methylnordihydrocodeinone
FS STEREOSEARCH
MF C24 H31 N O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

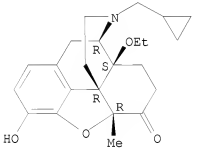


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 20 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 147847-14-1 REGISTRY
ED Entered STN: 28 May 1993
CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-14-ethoxy-3-hydroxy-5-methyl-, (5α)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 14-O-Ethyl-5-methylnaltrexone
CN 14-O-Ethyl-5β-di-O-methylnaltrexone
CN N-(Cyclopropylmethyl)-14-ethoxy-5-methylnordihydromorphinone
FS STEREOSEARCH
MF C23 H29 N O4
SR CA
LC STN Files: CA, CAPLUS, CASREACT, CHEMINFORMRX, TOXCENTER, USPATFULL

Absolute stereochemistry.



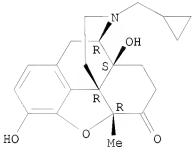
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 21 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 132406-78-1 REGISTRY

ED Entered STN: 01 Mar 1991
CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-5-methyl-, (5α)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5β-Methylnaltrexone
FS STEREOSEARCH
MF C21 H25 N O4
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.

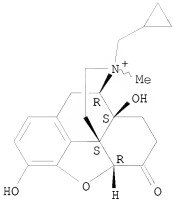


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 22 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 125292-47-9 REGISTRY
ED Entered STN: 09 Feb 1990
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, bromide, (5α)-(±)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (±)-N-Methylnaltrexone bromide
CN (±)-Naltrexone methobromide
FS STEREOSEARCH
MF C21 H26 N O4 . Br
SR CA
LC STN Files: CA, CAPLUS, PROUSDDR, SYNTHLINE, USPATFULL
CRN (785013-52-7)

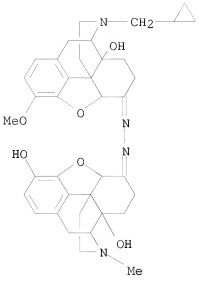
Relative stereochemistry.



● Br^-

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 23 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 110320-72-4 REGISTRY
ED Entered STN: 19 Sep 1987
CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-14-hydroxy-3-methoxy-, [(5α)-4,5-epoxy-3,14-dihydroxy-17-methylmorphinan-6-ylidene]hydrazone, (5α)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Oxymorphone-3-O-methylnaltrexone azine
MF C38 H44 N4 O6
SR CA
LC STN Files: CA, CAPLUS, CHEMCATS, MEDLINE

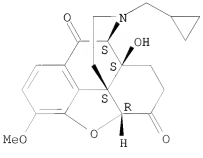


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 24 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 96445-13-5 REGISTRY
ED Entered STN: 25 May 1985
CN Morphinan-6,10-dione, 17-(cyclopropylmethyl)-4,5-epoxy-14-hydroxy-3-methoxy-, (5α)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 10-Ketonaltrexone-3-methyl ether
CN 10-Oxo-3-O-methylnaltrexone
FS STEREOSEARCH
MF C21 H23 N O5
LC STN Files: BEILSTEIN*, CA, CAPLUS
(*File contains numerically searchable property data)

Absolute stereochemistry.

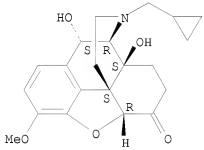


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 25 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 96445-12-4 REGISTRY
ED Entered STN: 25 May 1985
CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-10,14-dihydroxy-3-methoxy-, (5α,10α)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 10-Hydroxynaltrexone-3-methyl ether
CN 10α-Hydroxy-3-O-methylnaltrexone
FS STEREOSEARCH
MF C21 H25 N O5
LC STN Files: BEILSTEIN*, CA, CAPLUS
(*File contains numerically searchable property data)

Absolute stereochemistry.

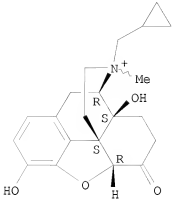


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 26 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 83387-25-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, (5α)- (CA INDEX NAME)
OTHER NAMES:
CN Methylnaltrexonium
CN N-Methylnaltrexone
FS STEREOSEARCH
MF C21 H26 N O4
CI COM
LC STN Files: ADISINSIGHT, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMCATS, DDFU, DRUGU, EMBASE, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, PROUSDDR, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

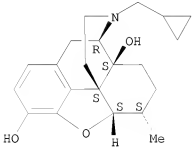
Absolute stereochemistry.



32 REFERENCES IN FILE CA (1907 TO DATE)
7 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
32 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 27 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 81394-72-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN Morphinan-3,14-diol, 17-(cyclopropylmethyl)-4,5-epoxy-6-methyl-, (5α,6α)- (CA INDEX NAME)
OTHER NAMES:
CN 6-Deoxy-6α-methylnaltrexone
FS STEREOSEARCH
MF C21 H27 N O3
LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL

Absolute stereochemistry.

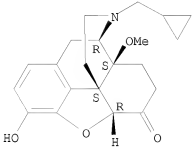


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 28 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 79823-83-9 REGISTRY
ED Entered STN: 16 Nov 1984
CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3-hydroxy-14-methoxy-, (5α)- (CA INDEX NAME)
OTHER NAMES:
CN 14-O-Methylnaltrexone
FS STEREOSEARCH
MF C21 H25 N O4
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXCENTER
(*File contains numerically searchable property data)

Absolute stereochemistry.

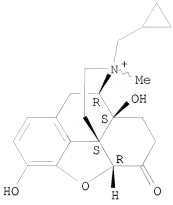


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

6 REFERENCES IN FILE CA (1907 TO DATE)
6 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 29 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 73232-53-8 REGISTRY
ED Entered STN: 16 Nov 1984
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, iodide (1:1), (5α)- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, iodide, (5α)- (9CI)
OTHER NAMES:
CN N-Methylnaltrexone iodide
CN Naltrexonium methiodide
FS STEREOSEARCH
MF C21 H26 N O4 . I
LC STN Files: CA, CAPLUS, IMSPATENTS, IMSRESEARCH, IPA, PROUSDDR, SYNTHLINE, TOXCENTER, USPATFULL
CRN (83387-25-1)

Absolute stereochemistry.

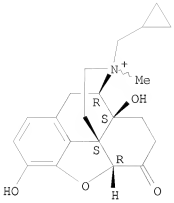


● I⁻

5 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 30 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 73232-52-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, bromide, (5α)- (CA INDEX NAME)
OTHER NAMES:
CN Methylnaltrexone
CN Methylnaltrexone bromide
CN MRZ 2663BR
CN N-Cyclopropylmethyl-noroxymorphone methobromide
CN N-Methylnaltrexone bromide
CN Naltrexone methobromide
CN Naltrexone methyl bromide
FS STEREOSEARCH
MF C21 H26 N O4 . Br
LC STN Files: ADISNEWS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, PROMT, PROUSDDR, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
CRN (83387-25-1)

Absolute stereochemistry.



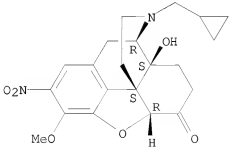
● Br^-

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

127 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
129 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 31 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 68026-72-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-14-hydroxy-3-methoxy-2-nitro-, (5α)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-Nitro-3-O-methylnaltrexone
CN O3-Methyl-2-nitronaltrexone
FS STEREOSEARCH
MF C21 H24 N2 O6
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

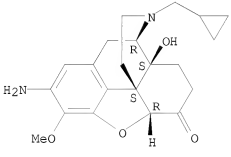


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 32 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 67829-20-3 REGISTRY
ED Entered STN: 16 Nov 1984
CN Morphinan-6-one, 2-amino-17-(cyclopropylmethyl)-4,5-epoxy-14-hydroxy-3-methoxy-, (5α)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-Amino-3-O-methylnaltrexone
CN 2-Amino-O3-methylnaltrexone
FS STEREOSEARCH
MF C21 H26 N2 O4
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

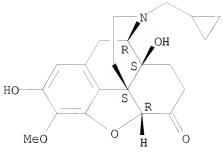


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 33 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 67829-18-9 REGISTRY
ED Entered STN: 16 Nov 1984
CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-2,14-dihydroxy-3-methoxy-, (5α)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-Hydroxy-3-O-methylnaltrexone
CN 2-Hydroxy-O3-methylnaltrexone
FS STEREOSEARCH
MF C21 H25 N O5
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



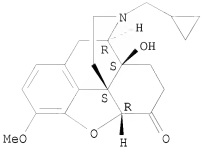
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 34 OF 34 REGISTRY COPYRIGHT 2008 ACS on STN
RN 16617-07-5 REGISTRY
ED Entered STN: 16 Nov 1984
CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-14-hydroxy-3-methoxy-, (5α)- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Morphinan-6-one, 17-(cyclopropylmethyl)-4,5α-epoxy-14-hydroxy-3-methoxy- (8CI)
OTHER NAMES:
CN 3-Methoxynaltrexone
CN 3-O-Methylnaltrexone
CN N-Cyclopropylmethylnoroxycodone
CN Naltrexone-3-methyl ether
CN O3-Methyl-(-)-naltrexone
FS STEREOSEARCH
DR 936213-37-5, 918502-32-6
MF C21 H25 N O4
CI COM
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, CHEMINFORMRX, IFICDB, IFIPAT, IFIUDB, RTECS*, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL, USPATOLD
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).

10821811



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

63 REFERENCES IN FILE CA (1907 TO DATE)
63 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file medicine
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	75.45	75.66

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FILE 'DDFU' ACCESS NOT AUTHORIZED

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FILE 'PASCAL' COULD NOT BE ENTERED

FILE 'PCTGEN' COULD NOT BE ENTERED

FILE 'PHARMAML' COULD NOT BE ENTERED

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FILE 'USGENE' COULD NOT BE ENTERED

FILE 'USPATFULL' ENTERED AT 14:40:48 ON 15 SEP 2008
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FILE 'USPATOLD' ENTERED AT 14:40:48 ON 15 SEP 2008
CA INDEXING COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 14:40:48 ON 15 SEP 2008
CA INDEXING COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)

=> s l1 or relistor
L2        1406 L1 OR RELISTOR

=> s solution
L3     4732829 SOLUTION

=> s l2 and l3

L4         112 L2 AND L3

=> s pH
L5     6276482 PH

=> s l4 and l5

L6          89 L4 AND L5

=> s EDTA or ethylenediaminetetraacetic acid or dipotassium edetate or disodium
edetate or edetate calcium disodium or sodium edetate or trisodium edetate or
potassium edetate
L7      415641 EDTA OR ETHYLENEDIAMINETETRAACETIC ACID OR DIPOTASSIUM EDETATE
               OR DISODIUM EDETATE OR EDETATE CALCIUM DISODIUM OR SODIUM EDETAT
               E OR TRISODIUM EDETATE OR POTASSIUM EDETATE

=> s l6 and l7

L8          16 L6 AND L7

=> dup re
'RE' IS NOT VALID HERE
Enter "REMOVE" to identify and remove duplicate answers.
Enter "IDENTIFY" to identify duplicate answers in the answer set.
Enter "ONLY" to identify and create an answer set containing only
duplicate records.
ENTER REMOVE, IDENTIFY, ONLY, OR (?):end

=> dup rem
ENTER L# LIST OR (END):l8
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, DRUGMONOG2, IMSPRODUCT'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L8
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L9 15 DUP REM L8 (1 DUPLICATE REMOVED)

=> d 19 1-15 ibib, kwic

L9 ANSWER 1 OF 15 USPATFULL on STN

ACCESSION NUMBER:	2008:221716 USPATFULL
TITLE:	Multi-arm polymer prodrugs
INVENTOR(S):	Zhao, Xuan, Beijing, CHINA Bentley, Michael D., Huntsville, AL, UNITED STATES Ren, Zhongxu, Madison, AL, UNITED STATES Viegas, Tacey X., Madison, AL, UNITED STATES
PATENT ASSIGNEE(S):	Nektar Therapeutics AL, Corporation, Huntsville, AL, UNITED STATES (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20080194612	A1	20080814
APPLICATION INFO.:	US 2008-69727	A1	20080211 (12)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2004-943799, filed on 17 Sep 2004, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2004-584308P	20040630 (60)
	US 2003-503673P	20030917 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	NEKTAR THERAPEUTICS, 201 INDUSTRIAL ROAD, SAN CARLOS, CA, 94070, US
NUMBER OF CLAIMS:	22
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	9 Drawing Page(s)
LINE COUNT:	2292

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . or segment will transmit at least about 75%, more preferably at least about 95% of light, transmitted by the same solution after filtering. On a weight basis, a water-soluble polymer or segment thereof will preferably be at least about 35% (by. . .

DETD . . . phospholipids such as lecithin and other phosphatidylcholines, phosphatidylethanolamines, fatty acids and fatty esters, steroids (e.g., cholesterol)), and chelating agents (e.g., EDTA, zinc and other such suitable cations). Other pharmaceutical excipients and/or additives suitable for use in the compositions according to the. . .

DETD . . . In general, the compositions are prepared by bringing the active compound into association with a liquid carrier to form a solution or a suspension, or alternatively, bring the active compound into association with formulation components suitable for forming a solid, optionally. . .

DETD A syrup may be made by adding the active compound to a concentrated aqueous solution of a sugar, for example sucrose, to which may also be added any accessory ingredient(s). Such accessory ingredients may include. . .

DETD . . . purified aqueous solutions of the active agent with preservative agents and isotonic agents. Such formulations are preferably adjusted to a pH and isotonic state compatible with the nasal mucous membranes.

DETD Ophthalmic formulations are prepared by a similar method to the nasal spray, except that the pH and isotonic factors are preferably adjusted to match that of the eye.

DETD Pharmaceutical formulations are also provided which are suitable for administration as an aerosol, by inhalation. These formulations comprise a solution or suspension of the desired polymer conjugate or a salt thereof. The desired formulation may be placed in a small. . . .

DETD . . . t-Boc-Glycine (0.3408 mmoles), and 0.021 g DMAP (0.1704 mmoles) were dissolved in 13 mL of anhydrous dichloromethane (DCM). To the solution was added 0.070 g DCC (0.3408 mmoles) dissolved in 2 mL of anhydrous DCM. The solution was stirred overnight at room temperature. The solid was removed through a coarse frit, and the solution was washed with 10 mL of 0.1N HCL in a separatory funnel. The organic phase was further washed with 10. . . .

DETD 0.1 g t-Boc-Glycine-Irinotecan (0.137 mmoles) was dissolved in 7 mL of anhydrous DCM. To the solution was added 0.53 mL trifluoroacetic acid (6.85 mmoles). The solution was stirred at room temperature for 1 hour. The solvent was removed using rotary evaporation. The crude product was dissolved. . .

DETD . . . 0.488 mmoles), and 0.0658 g 2-hydroxybenzyltriazole (HOBT, 0.488 mmoles) were dissolved in 60 mL anhydrous methylene chloride. To the resulting solution was added 0.282 g 1,3-dicyclohexylcarbodiimide (DCC, 1.3664 mmoles). The reaction mixture was stirred overnight at room temperature. The mixture was. . .

DETD . . . g, 0.1 mol) and NaHCO.sub.3 (12.6 g, 0.15 mol) were added to 100 mL CH.sub.2Cl.sub.2 and 100 mL H.sub.2O. The solution was stirred at RT for 10 minutes, then di-tert-butyl dicarbonate (21.8 g, 0.1 mol) was added. The resulting solution was stirred at RT overnight, then extracted with CH.sub.2Cl.sub.2 (3+100 mL). The organic phases were combined and dried over anhydrous. . .

DETD . . . (14.6 g, 120 mmol) were dissolved in 200 ml anhydrous CH.sub.2Cl.sub.2. Triphosgene (5.91 g, 20 mmol) was added to the solution while stirring at room temperature. After 20 minutes, the solution was added to a solution of irinotecan (6.0 g, 10.2 mmol) and DMAP (12.2 g, 100 mmol) in anhydrous CH.sub.2Cl.sub.2 (200 mL). The reaction was stirred at RT for 2 hrs, then washed with HCl solution (pH=3, 2 L) to remove DMAP. The organic phases were combined and dried over anhydrous sodium sulfate. The dried solution was evaporated under vacuum and subjected to silica gel column chromatography (CH.sub.2Cl.sub.2:CH.sub.3OH=40:1.about.10:1) to afford 2-(2-t-Boc-aminoethoxy)ethoxycarbonyl-irinotecan (2) (4.9 g, 6.0 mmol,. . .

DETD . . . 5.75 mmol) was dissolved in 60 mL CH.sub.2Cl.sub.2, and trifluoroacetic acid (TFA) (20 mL) was added at RT. The reaction solution was stirred for 2 hours. The solvents were removed under vacuum and the residue was added to ethyl ether and. . .

DETD . . . (2.85 g, 3.44 mmol) was dissolved in 12 mL DMF and treated with 0.6 mL TEA, then added to a solution of 4-arm-PEG.sub.20k-SCM. The reaction was stirred at RT for 12 hrs then precipitated in Et.sub.2O to yield a solid product, which was dissolved in 500 mL IPA at 50° C. The solution was cooled to RT and the resulting precipitate collected by filtration to give 4-arm-PEG.sub.20k-glycine-irinotecan (4) (16.2 g, drug content 7.5%. . .

DETD . . . (2.85 g, 3.44 mmol) was dissolved in 12 mL DMF and treated with 0.6 mL TEA, then added to the solution of 4-arm-PEG.sub.40k-

SCM. The reaction was stirred at RT for 12 hrs and then precipitated in Et.sub.2O to get solid product, which was dissolved in 1000 mL isopropyl alcohol (IPA) at 50° C. The solution was cooled to RT and the precipitate collected by filtration to gave 4-arm-PEG.sub.40k-glycine-irinotecan (4) (g, drug content 3.7% based on. . .

IT 76-41-5DP, Oxymorphone, polymer derivs. 76-42-6DP, Oxycodone, polymer derivs. 76-57-3DP, Codeine, polymer derivs. 79-39-0DP, Methacrylamide, hydroxyalkyl derivs., polymers, drug conjugates 79-41-4DP, Methacrylic acid, hydroxyalkyl esters, polymers, drug conjugates 124-94-7DP, Triamcinolone, polymer derivs. 465-65-6DP, Naloxone, polymer derivs. 4291-63-8DP, Cladribine, polymer derivs. 9002-89-5DP, Polyvinyl alcohol, drug derivs. 9003-01-4DP, Polyacrylic acid, drug derivs. 9003-39-8DP, Polyvinylpyrroiidone, drug derivs. 15663-27-1DP, cis-Platin, polymer derivs. 28902-82-1DP, Poly(N-acryloylmorpholine), drug derivs. 41575-94-4DP, Carboplatin, polymer derivs. 51333-22-3DP, Budesonide, polymer derivs. 61825-94-3DP, Oxaliplatin, polymer derivs. 73232-52-7DP, Methylnaltrexone, polymer derivs. 75607-67-9DP, Fludarabine phosphate, polymer derivs. 85721-33-1DP, Ciprofloxacin, polymer derivs. 90566-53-3DP, Fluticasone, polymer derivs. 95058-81-4DP, Gemcitabine, polymer derivs. 135729-61-2DP, Palonosetron, polymer derivs. 151096-09-2DP, Moxifloxacin, polymer derivs. 848779-38-4P (water-soluble multi-arm polymer prodrugs)

L9 ANSWER 2 OF 15 USPATFULL on STN

ACCESSION NUMBER:	2008:221715 USPATFULL			
TITLE:	Modulation of Cell Barrier Dysfunction			
INVENTOR(S):	Alverdy, John C., Glenview, IL, UNITED STATES			
	Moss, Jonathan, Chicago, IL, UNITED STATES			
	Lingen, Mark W., Oak Park, IL, UNITED STATES			
	Singleton, Patrick A., Chicago, IL, UNITED STATES			
	Garcia, Joe G.N., Chicago, IL, UNITED STATES			

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20080194611	A1	20080814	
APPLICATION INFO.:	US 2006-914984	A1	20060506	(11)
	WO 2006-US21604		20060506	
			20080214	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	WO 2005-US7892	20060307
	US 2005-687568P	20050603 (60)
	US 2005-731009P	20051028 (60)
	US 2006-760851P	20060120 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	MICHAEL BEST & FRIEDRICH LLP, ONE SOUTH PINCKNEY STREET, P O BOX 1806, MADISON, WI, 53701, US
NUMBER OF CLAIMS:	40
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	21 Drawing Page(s)
LINE COUNT:	5612

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . to ambient environmental cues. In general such physico-chemical

cues signal environmental stress or adversity, such as changes in redox status, pH, osmolality, and the like. For example, P. aeruginosa and other bacteria can express a lectin/adhesin PA-I. The distribution of PA-I. . .

DETD . . . of which are herein incorporated herein by reference in their entireties. The pharmaceutical compositions of the invention may comprise a solution balanced in viscosity, electrolyte profile and osmolality, comprising an electrolyte, dextran-coated L-glutamine, dextran-coated inulin, lactulase, D-galactose, N-acetyl D-galactosamine and 5-20%. . .

DETD . . . include solutions or suspensions which may contain, for example, suitable non-toxic diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides and fatty acids, including oleic acid.. . .

DETD The compound of formula (II) has low solubility in water except at low or high pH conditions. Zwitterionic character may be inherent to the compound, and may impart desirable properties such as poor systemic absorption and. . .

DETD . . . to room temperature. The product may be isolated by the addition to the reaction mixture of a saturated sodium chloride solution to quench any residual lithium reagent. The organic layer may be separated and further purified if desired to provide the. . .

DETD . . . generally from about 50° C. and 150° C. The product thus formed may be isolated by basifying an acidic aqueous solution of the salt form of the product and extracting the aqueous solution with a suitable water immiscible solvent. The resulting residue following evaporation can then be further purified if desired.

DETD . . . an inert atmosphere, such as nitrogen or argon. Generally, a slight excess of n-butyllithium may be added to a stirring solution of the 1-alkyl-4-(3-alkoxyphenyl)-tetrahydropyridine in THF cooled to a temperature in the range of from about is -50° C. to about. . . 10 to 30 minutes followed by the addition of approximately from 1.0 to 1.5 equivalents of methyl halide to the solution while maintaining the temperature of the reaction mixture below 0° C. After about 5 to 60 minutes, water may be. . .

DETD . . . be the preferred solvent, other non-nucleophilic solvents, such as acetone and acetonitrile can also be employed in this reaction. The pH of this solution may be adjusted to approximately 3.0 to 4.0 with an acid that provides a non-nucleophilic anion. Examples of such acids. . . acids such as methanesulfonic acid and p-toluenesulfonic acid, phosphoric acid, and tetrafluoroboric acid, with sulfuric acid being preferred. To this solution may be added one equivalent of a 1-alkyl-4-methyl-4-(3-alkoxyphenyl)tetrahydropyridine, typically dissolved in aqueous sulfuric acid, and the pH of the solution may be readjusted with the non-nucleophilic acid or a suitable secondary amine. The pH is preferably maintained in the range of from about 1.0 to 5.0, with a pH of about 3.0 to 3.5 being more preferred during the reaction. The reaction is substantially complete after about 1 to. . . preferably about 70° C. The reaction may then be cooled to approximately 30° C., and added to a sodium hydroxide solution. This

solution may then be extracted with a water immiscible organic solvent, such as hexane or ethyl acetate, and the organic phase,. . .

DETD . . . the corresponding phenol. This reaction may be generally carried out by reacting the compound in a 48% aqueous hydrobromic acid solution. This reaction may be substantially complete after about 30 minutes to 24 hours when conducted at a temperature of from. . . more preferably at the reflux temperature of the reaction mixture. The mixture may then be worked up by cooling the solution, followed by neutralization with base to an approximate pH of 8. This aqueous solution may be extracted with a water immiscible organic solvent. The residue following evaporation of the organic phase may then be. . .

DETD . . . freeze drying technique which yields a powder of the active ingredient, plus any additional desired ingredient from the previously sterilized solution thereof.

DETD In vitro studies demonstrated that pH, osmolality, and norepinephrine did not change PA-I expression, while opioids, interferon-gamma, C4-HSL, and media from hypoxic and hyperthermia intestinal epithelial. . .

DETD . . . changes in the local microenvironment, P. aeruginosa strain PA-27853 and reporter strains (PLL-EGFP) were exposed to ambient hypoxia (0.3% O.sub.2), pH changes (6-8), and 80% CO.sub.2. None of these conditions induced PA-I expression. In addition, reporter strains exposed to the blood. . .

DETD . . . a predetermined time. Next, the supernatant is removed and the bacterial cell pellet is lysed by the addition of lysis solution directly into the well. The entire 384-well plate is then spun down (4000 g) and the supernatant transferred to an. . .

DETD . . . 10 minutes of ischemia (segmental artery clamp) followed by 10 minutes of reperfusion. Luminal perfusion with 2 ml of Ringers solution is performed to collect the luminal contents before and after I/R. Luminal contents, the homogenized intestinal segment, and blood are. . .

DETD . . . segments subjected to sham ischemia (no clamp), 10 minutes of ischemia, and 10 minutes of reperfusion is perfused with Ringers solution and the timed aliquots of the perfusates is collected from both IFN-γ knockout mice and their wild-type cohorts. Use of. . .

DETD . . . the most cost effective and rapid approach. For non-proteinaceous PA-I inducing compounds, lipid assays are contemplated that involve adjusting fraction pH to 3.5, followed by HPLC using, e.g., a Sep-Pak C.sub.18 column. Eluted samples are trapped on a fraction collector, evaporated. . .

DETD Samples (0.5 μL) are mixed with an equal volume of a 5 mg/mL solution of α-cyanohydroxycinnamic acid in 30% acetonitrile in water with 0.1% TFA and are then manually spotted onto a 192 spot. . .

DETD The protein extract sample is diluted in 50 mM ammonium carbonate buffer, pH 8.5, containing 0.1% Rapigest SF acid labile detergent (Waters Corp, Millford, Mass.). The sample is heated to 100° C. for. . . halted by adding PMSF to final concentration of 1 mM. After digestion, 10 μL of TFA is added to the solution and the sample is incubated for 45 minutes at 37° C. to destroy the acid labile Rapigest detergent.

DETD Fractions are pH adjusted to 3.5, and run across a Sep-Pak C.sub.18 column on a HPLC system (Millipore corp., Milford, Mass.). The

columns. . .
DETD . . . expressing SGLT1 were maintained in DMEM with 25 mM glucose (high-glucose DMEM) with 10% fetal calf serum, 15 mM HEPES, pH 7.4, and 0.25 mg/ml geneticin, as previously described (Turner J R et al., Am J Physiol 273: C1378-1385, 1997). Caco-2. . .
DETD . . . measured by fluorescence, within 1 h of incubation with Caco-2 cells exposed to either hypoxia or normoxic recovery. The media pH in all experimental conditions was measured at all time points and demonstrated no significant difference among control, hypoxia, and normoxic recovery groups because all media were buffered (data not shown). However, to show that the pH of media did not influence fluorescence in PA27853/PLL-EGFP, strains were incubated in media at pH 6.5, 7.4, and 7.7. The percent change in fluorescence was not different among groups (6.5=106±10, 7.4=100±12, 7.7=112±12; P=not significant). Similarly,. . .
DETD . . . genes on and off in response to selected environmental cues. Although it is well established that environmental cues such as pH, redox state, and nutrient composition can activate virulence gene expression in bacteria through a variety of membrane-bound biosensor kinases, there. . .
DETD Immunoprecipitation and Immunoblotting--Cellular materials from treated or untreated HPMVEC were incubated with IP buffer (50 mM HEPES (pH 7.5), 150 mM NaCl, 20 mM MgCl.sub.2, 1% Nonidet P-40 (NP-40), 0.4 mM Na.sub.3VO.sub.4, 40 mM NaF, 50 μM okadaic. . .
DETD . . . Receptor Phosphorylation/Dephosphorylation--The S1P.sub.3 receptor phosphorylation/dephosphorylation reaction was carried out in 50 μl of the reaction mixture containing 40 mM Tris-HCl (pH 7.5), 2 mM EDTA, 1 mM dithiothreitol, 7 mM MgCl.sub.2, 0.1% CHAPS, 100 μM ATP, purified enzymes (i.e. 100 ng of recombinant active Src. . .
DETD . . . control (untreated) mice were formalin-fixed, 5 micron paraffin sections were obtained, hydrated and epitope retrieval was performed (DakoCytomation Target Retrieval Solution, pH=6.0, DakoCytomation, Carpinteria, Calif.). The sections were then histologically evaluated by either anti-mu opioid receptor, anti-RPTPμ or anti-S1P3 receptor antibody and. . .
DETD Determination of Bronchioalveolar Lavage Protein--Bronchioalveolar lavage (BAL) was performed by an intratracheal injection of 1 cc of Hank's balanced salt solution followed by gentle aspiration. The recovered fluid was processed for protein concentration (BCA Protein Assay Kit; Pierce Chemical Co., Rockford,. . .
IT 110-89-4D, Piperidine, N-alkyl carboxylate derivs. 468-10-0D, Morphinan, quaternary or tertiary derivs. 73232-52-7, Methylnaltrexone 156053-89-3, Alvimopan
(opioid antagonists to attenuate endothelial cell proliferation and migration)

L9 ANSWER 3 OF 15 USPATFULL on STN
ACCESSION NUMBER: 2008:80843 USPATFULL
TITLE: Formulations for parenteral delivery of compounds and uses thereof
INVENTOR(S): Shah, Syed M., East Hanover, NJ, UNITED STATES
Ofslager, Christian, Newburgh, NY, UNITED STATES
Fawzi, Mahdi B., Morristown, NJ, UNITED STATES
Bazhina, Natalyia, Orangeburgh, NY, UNITED STATES
PATENT ASSIGNEE(S): Wyeth, Madison, NJ, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20080070975	A1	20080320
APPLICATION INFO.:	US 2007-890034	A1	20070803 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-835574P	20060804 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	CHOATE, HALL & STEWART LLP/WYETH, PATENT GROUP, TWO INTERNATIONAL PLACE, BOSTON, MA, 02110, US	
NUMBER OF CLAIMS:	70	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	5 Drawing Page(s)	
LINE COUNT:	3251	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . selected from at least methylnaltrexone, or a pharmaceutically acceptable salt thereof, and a calcium salt chelating agent in an aqueous solution.

SUMM . . . provided together as a calcium salt chelating agent. In some embodiments, a calcium salt chelating agent is selected from calcium ethylenediaminetetraacetic acid (EDTA), calcium diethylenetriaminepentaacetic acid (DTPA), calcium hydroxyethylenediaminetriacetic acid (HEDTA), calcium ethylene glycol-bis-(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), calcium nitrilotriacetic acid (NTA), calcium citrate, and calcium salt derivatives thereof. In some embodiments a calcium salt chelating agent is calcium EDTA.

SUMM . . . isotonic agent, and an aqueous solvent. In some embodiments, a formulation comprises methylnaltrexone or a pharmaceutically acceptable salt thereof, calcium EDTA, glycine, and sodium chloride, in an aqueous solution.

DRWD . . . 2',2-bis methylnaltrexone in the presence of iron at 40° C. (FIG. 1A) and room temperature, 25° (FIG. 1B). Both calcium EDTA and sodium EDTA are effective inhibitors of formation of the 2',2' bis methylnaltrexone degradant.

DRWD . . . methylnaltrexone in the presence of iron at 40° C. (FIG. 2A) and room temperature, 25° (FIG. 2B) was assessed. Calcium EDTA but not sodium EDTA is an effective inhibitor of formation of the 7-dihydroxy-methylnaltrexone degradant. The effect of CaEDTA on the formation of 7-dihydroxy methylnaltrexone in solution following one month storage at room temperature (FIG. 2C) and at 40° C. (FIG. 2D) was assessed. The presence of. . .

DRWD FIG. 3A and FIG. 3B: Effect of CaEDTA in methylnaltrexone solution on the formation of a methylnaltrexone degradant having an RRT 0.79 ("the 0.79 degradant"). The effect of CaEDTA and NaEDTA. . . formation of the 0.79 degradant at room temperature, 25° (FIG. 3A) and at 40° C. (FIG. 3B) was assessed. Calcium EDTA was not effective at inhibiting formation of the 0.79 degradant, and may increase levels of degradant formation.

DETD . . . . comprises methylnaltrexone, a calcium salt chelating agent, an isotonic agent, a stabilizing agent, and a carrier. In some embodiments, the pH of the formulation is between about a pH of 2 to about a pH of 5.

DETD . . . provides formulations that are stable formulations for parenteral administration of methylnaltrexone compositions. Formulations provided for parenteral administration may include sterile solution for injection, sterile suspension for injection, sterile emulsions, and dispersions.

DETD For example, in some embodiments, formulations comprise methylnaltrexone, and a calcium salt-chelating agent in an isotonic solution. In some embodiments, formulations comprise methylnaltrexone, a calcium salt chelating agent, and a stabilizing agent in an isotonic solution.

DETD . . . agents include any pharmaceutically acceptable chelating agents and salts thereof. Examples of chelating agents include, but are not limited to ethylenediaminetetraacetic acid (also synonymous with EDTA, edetic acid, versene acid, and sequestrene), and EDTA derivatives, such as sodium EDTA, and potassium EDTA, diammonium EDTA, dipotassium EDTA, disodium EDTA, TEA-EDTA, tetrasodium EDTA, tripotassium EDTA, trisodium EDTA, HEDTA, and trisodium HEDTA, and related salts thereof. Other chelating agents include niacinamide and derivatives thereof and sodium desoxycholate and. . . monohydrate. Derivatives of citric acid include anhydrous citric acid and trisodium citrate-dihydrate. In some embodiments, chelating agent is selected from EDTA or an EDTA derivative or EGTA or an EGTA derivative. In some embodiments chelating agent is EDTA disodium such as, for example, EDTA disodium hydrate.

DETD . . . agents and calcium salts thereof. Common calcium salt chelating agents include, but are not limited to calcium ethylenediaminetetra acetic acid (EDTA) and calcium salt EDTA derivatives, calcium ethylene glycol-bis-(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA) and calcium salt EGTA derivatives, calcium diethylenetriaminepentaacetic acid (DTPA) and calcium salt DTPA derivatives,. . . and calcium salt NTA derivatives, and calcium citrate and derivatives thereof. In some embodiments, chelating agent is selected from calcium EDTA or a calcium salt EDTA derivative or calcium EGTA or a calcium salt EGTA derivative. In some embodiments chelating agent is calcium EDTA disodium such as, for example, calcium EDTA disodium hydrate.

DETD . . . the formulation comprises methylnaltrexone, an isotonic agent which is sodium chloride, and a calcium salt chelating agent which is calcium EDTA or a calcium salt EDTA derivative. In some embodiments, the EDTA is calcium EDTA disodium.

DETD . . . embodiments, the formulation comprises water for injection. In some embodiments, formulations comprise methylnaltrexone or a pharmaceutically acceptable salt thereof, calcium EDTA or a calcium salt EDTA derivative, water for injection, and sodium chloride in an amount such that the final solution is isotonic (e.g., 0.1%, 0.25%, 0.45% 0.65%, 0.9% sodium chloride). In some embodiments, the sodium chloride is present in an. . .

DETD . . . In some embodiments, the formulation comprises glycine. In some embodiments, glycine comprises glycine-HCl. In some embodiments, formulations comprise methylnaltrexone, calcium EDTA or a calcium salt EDTA derivative, water for injection, sodium chloride in an amount such that the final concentration is 6.5 mg/mL isotonic sodium chloride,. . .

DETD In certain embodiments, a stabilizing agent is added to the formulation

in an amount sufficient to adjust and maintain the pH of the formulation. Thus, in some embodiments, a stabilizing agent acts as a buffer function in addition to its role. . . as a stabilizer. In some embodiments, a stabilizing agent may act as a buffer agent, so as to maintain the pH of the formulation. In certain embodiments, the pH is between about pH 2.0 and about pH 6.0. In some embodiments, the pH of the formulation is between about pH 2.6 and about pH 5.0. In some embodiments, the pH of the formulation is between about pH 3.0 and about pH 4.0. In some embodiments, the pH of the formulation is between about pH 3.4 and about pH 3.6. In some embodiments, the pH of the formulation is about pH 3.5.

DETD In some embodiments, provided formulations comprise methylnaltrexone, calcium EDTA or a calcium salt EDTA derivative, water for injection, sodium chloride in an amount such that the final concentration is 6.5 mg/mL isotonic sodium chloride, glycine, and the pH of the formulation is between about pH 3.0 and about pH 4.0. In some embodiments, formulations comprise methylnaltrexone or a pharmaceutically acceptable salt thereof, calcium EDTA or a calcium salt EDTA derivative, water for injection, sodium chloride in an amount such that the final concentration is 6.5 mg/mL isotonic sodium chloride, glycine, and the pH of the formulation is between about pH 3.4 and about pH 3.6. In some embodiments, formulations comprise methylnaltrexone bromide, calcium EDTA or a calcium salt EDTA derivative, water for injection, sodium chloride in an amount such that the final concentration is 6.5 mg/mL isotonic sodium chloride, and glycine, and the formulation has a pH of about 3.5. In certain embodiments, the pH is adjusted with glycine. In some embodiments, glycine is glycine HCl.

DETD In some embodiments, provided formulations comprise methylnaltrexone bromide, calcium EDTA, water for injection, isotonic sodium chloride, glycine HCl, and the formulation has a pH between about 3.4 and about 3.6. In some embodiments, provided formulations comprise methylnaltrexone bromide at a concentration about 20 mg/mL, calcium EDTA at a concentration about 0.4 mg/mL, sodium chloride in an amount such that the final concentration is 6.5 mg/mL isotonic sodium chloride, and glycine HCl at a concentration about 0.3 mg/mL, and the formulation has a pH of about 3.5. In some embodiments, formulations comprise methylnaltrexone bromide at a concentration about 10 mg/mL, calcium EDTA at a concentration about 0.2 mg/mL, sodium chloride in an amount such that the final concentration is 3.25 mg/mL isotonic sodium chloride, and glycine HCl at a concentration about 0.15 mg/mL, and the formulation has a pH of about 3.5.

DETD One of ordinary skill in the art will recognize that additional pH adjustments may be required to ensure that a provided formulation has desired pH. Thus, in certain embodiments, further pH adjustment is performed with hydrochloric acid and/or sodium hydroxide.

DETD In one embodiment, the formulation is in a vial filled with methylnaltrexone solution, where the solution comprises at least one active compound which is methylnaltrexone, and a calcium salt chelating agent, in an isotonic solution. In one embodiment, a provided formulation is in a vial where the vial is filled

with a provided formulation, as. . .

DETD . . . of the container to a subject, or, alternatively to a second container for mixing and/or dilution of contents with another solution. A dose-concentrate of a provided formulation can be in a sealed container holding an amount of the pharmaceutical formulation of. . . over a standard treatment interval such as immediately upon dilution, or up to 24 hours after dilution, as necessary. A solution for intravenous administration can be prepared, for example, by adding a dose-concentrate formulation to a container (e.g., glass or plastic. . .

DETD . . . inlet and outlet means and having standard (e.g., 25 mL, 50 mL, 100 mL and 150 mL) capacities. Dose concentrate solution of a pharmaceutical formulation of the invention is added to a unit dosage IV container in an amount to achieve. . .

DETD . . . as follows: dry components of a formulation, including active compound (e.g., methylnaltrexone bromide), and calcium salt chelating agent (e.g., calcium EDTA) are dissolved in an appropriate solvent (e.g., an isotonic solution (e.g., isotonic sodium chloride for injection)). Optionally, additional dry and/or wet ingredients (e.g., solvent (e.g., water)), stabilizing agent, or surfactant,. . .

DETD . . . as follows: dry components of a formulation, including active compound (e.g., methylnaltrexone bromide), and calcium salt chelating agent (e.g., calcium EDTA) are dissolved in an appropriate solvent (e.g., an isotonic solution (e.g., isotonic sodium chloride for injection)). Alternatively, dry components of a formulation, including active compound (e.g., methylnaltrexone bromide), and isotonic. . . sodium chloride) are dissolved in an aqueous solvent (e.g., water for injection) to generate an active compound in an isotonic solution (e.g., methylnaltrexone in isotonic sodium chloride for injection), followed by further addition and dissolution of calcium salt chelating agent (e.g., calcium EDTA) to the solution. Next, the pH of the solution may be adjusted. For example, addition of glycine may adjust the pH to the desired level. For example, addition of glycine HCl may be utilized for addition to the solution to adjust pH to a desired pH (e.g., pH 3-4, pH 3.4-3.6, pH 3.5). Optionally, additional dry and/or wet ingredients (e.g., solvent (e.g., water), stabilizing agent (e.g., glycine), or surfactant, may be added.. . .

DETD . . . include, but are not limited to surfactants, preservatives, diluents, buffers, co-solvents, etc. Typical amounts of additional excipients added to a solution may include, for example, buffers about 10% to about 90%, co-solvents about 1% to about 50%, diluents about 1% to. . .

DETD . . . may include, for example in the case of injection preparations, a sterilizing filtration and/or an ultra filtration of the processing solution before packaging to eliminate microorganisms or other contaminating matter from the processing solution.

DETD . . . The distributing process includes, for example in the case of vial packaging, a process distributing a suitable volume of the solution into vials taking the concentration of methylnaltrexone into consideration in order that contained products carry a desired amount of methylnaltrexone.

DETD . . . formulation in a dilution package or container wherein a

needle-less exchange mechanism allows for combination of formulation and with isotonic solution for preparation for intravenous administration. For example, in certain non-limiting examples, a formulation of the invention may be utilized in. . .

DETD Previously, at least three degradation products were demonstrated from HPLC analysis in 20 mg/mL isotonic saline solution (identified as RRT peaks at about 0.72, 0.89, and 1.48 when products were analyzed by HPLC). See, e.g., US Patent. . .

DETD . . . A: 95:5 (v/v) 0.1% TFA in Water/Methanol
Solvent B: 35:65 (v/v) 0.1% TFA in Water/Methanol
Sample Solvent: 0.05M Dibasic Sodium Phosphate pH 6.8

Gradient Program:	Time (Min)	% Mobile Phase A
	0	100
	45	50
	45.1	100
	60	100

Column Temperature: 50° C.
Method. . . A: 95:5 (v/v) 0.1% TFA in Water/Methanol
Solvent B: 25:75 (v/v) 0.1% TFA in Water/Methanol
Sample Solvent: 0.05M Dibasic Sodium Phosphate pH 6.8

Gradient Program:	Time (Min)	% Mobile Phase A
	0	100
	45	50
	45.1	100
	60	100

Method B: (strength)
Column: Prodigy. . . A: 95:5 (v/v) 0.1% TFA in Water/Methanol
Solvent B: 25:75 (v/v) 0.1% TFA in Water/Methanol
Sample Solvent: 0.05M Dibasic Sodium Phosphate pH 6.8

Gradient Program:	Time (Min)	% Mobile Phase A
	0	95
	1.0	85
	12.0	50
	15.0	95
	20.0	95

DETD Inhibition of metal-catalyzed formation of 2,2'bis methylnaltrexone. We have found Fe3.sup.+ facilitates degradation of methylnaltrexone bromide in solution, resulting in formation of a 2,2'bis methylnaltrexone degradant. We have found by HPLC analysis (Method B) the 2,2'bis methylnaltrexone degradant. . . from several sources. For example, it can be leached from stainless steel process equipment, syringe needles, stoppers and amber vials. EDTA, as a metal chelating agent sequesters the available Fe.sup.3+ in the solution, thereby preventing catalysis of the undesirable metal-catalyzed reactions. Methylnaltrexone solutions were prepared in 0.9% NaCl, in the presence of iron and various concentrations of sodium EDTA and calcium EDTA. Used throughout the experiments

sodium EDTA is EDTA disodium dihydrate, and the terms sodium EDTA, EDTA disodium dihydrate, and NaEDTA are used interchangeably throughout. Used throughout the experiments calcium EDTA is calcium EDTA disodium, and the terms calcium EDTA, calcium EDTA disodium, and CaEDTA are used interchangeably throughout. Formation of 2,2'bis methylnaltrexone was assessed at room temperature as well as at 40° C. Addition of either sodium or calcium EDTA solution was effective at inhibiting formation of the 2,2'bis methylnaltrexone degradant. See FIG. 1A and FIG. 1B. Thus, chelating action will facilitate methylnaltrexone bromide stability in solution at room temperature.

DETD Inhibition of metal-catalyzed formation of 7-dihydroxy-methylnaltrexone. We have found EDTA inhibits metal catalyzed formation of a 7-dihydroxy-methylnaltrexone degradant in methylnaltrexone solution. We have found by HPLC analysis (Method B) the 0.67 peak degradant to be the presence of 7-dihydroxy methylnaltrexone. Methylnaltrexone solutions were prepared in 0.9% NaCl, in the presence of iron and various concentrations of EDTA. Formation of 7-dihydroxy methylnaltrexone was assessed. Addition of either EDTA solution was effective at inhibiting formation of the 7-dihydroxy methylnaltrexone degradant. See Table 1.

TABLE 1

Peak area of RRT 0.67 degradant. . .

DETD . . . Na.sup.2+ chelating agent. Methylnaltrexone solutions were prepared in 0.9% NaCl, in the presence of iron and various concentrations of sodium EDTA and calcium EDTA. Formation of 7-dihydroxy-methylnaltrexone was assessed at room temperature as well as at 40° C. Addition of calcium EDTA solution was highly effective at inhibiting formation of the 7-dihydroxy-methylnaltrexone degradant at both temperatures. See FIG. 2A and FIG. 2B. Use of calcium facilitates methylnaltrexone bromide stability in solution at room temperature. Furthermore, long term storage of solution at either room temperature or 40° C./75% relative humidity also demonstrated stabilization and inhibition of 7-dihydroxy methylnaltrexone degradant formation when calcium EDTA was present. After one month at room temperature, resultant production of 7-dihydroxy-methylnaltrexone was reduced from 0.34% to 0.11% in the presence of calcium EDTA. Furthermore, at 40° C./75% RH, degradant was reduced from 0.64% in saline solution alone to 0.14% in sample containing calcium EDTA. See FIG. 2C and FIG. 2D.

DETD Preparation of an Improved Room Temperature Methylnaltrexone Formulation. Our results have shown a methylnaltrexone formulation comprising a saline solution of active compound plus calcium salt-chelating agent results in a formulation having improved room temperature stability characteristics. Preparation of such improved formulations comprise use of the following exemplary components:

Active	Methylnaltrexone bromide	(5 to 40 mgs)
Chelating agent	Calcium EDTA	(0.05 to 1.5 mgs)
Isotonic Delivery Vehicle	0.9% Normal Saline	(1 to 1.25 mL)

DETD . . . or 30 mgs of methylnaltrexone bromide were dissolved in 0.9% sodium chloride; and 0.24 mg or 0.5 mg of calcium EDTA were also dissolved in the solution. Resulting solutions were prepared and filter sterilized at ambient conditions, and resulting formulations filled into clear glass vials, ampoules, syringes or auto-dispensers.

TABLE 2

Formulation

INGREDIENTS	0.6 mL/VIAL	1.25 mL/VIAL
Methylnaltrexone bromide	20 mg	30 mg
Calcium EDTA, NF	0.24 mg	0.5 mg
Sodium Chloride	0.65%	0.65%

DETD Inhibition of pH Dependent Degradation of Methylnaltrexone Formulations

DETD Inhibition of pH influenced formation of methylnaltrexone degradants. We have found in the presence of Ca.sup.2+ and EDTA , degradation of methylnaltrexone bromide in solution occurs under some stability conditions, resulting in formation of a third-methylnaltrexone degradant. We have found by HPLC analysis (Method B). . .

DETD . . . lower at room temperature in the CaEDTA formulation described in Example 2 above as compared to refrigerated methylnaltrexone in saline solution. Methylnaltrexone solution as described in Example 2 containing CaEDTA was compared to a control refrigerated methylnaltrexone solution in saline and formulations assessed for production of 0.79 degradant formation (room temperature CaEDTA 0.03% vs. refrigerated control saline 0.06%). See FIG. 3A and FIG. 3B. Use of calcium EDTA appears to facilitate production of the 0.79 degradant under our accelerated stability conditions, however, as it was found at 40°. . .

DETD We found reduction in pH as well as the presence of glycine resulted in stabilization of the 0.79 degradant. Table 4, summarizes the formulation stability without pH control at 70° C. The formulation has a pH of 5.6. The data confirms that a formulation containing Ca EDTA does limit the formation of 0.67 and RRT 1.55 but does not reduce RRT 0.79. After only a few days. . .

DETD We tested whether the 0.79 degradant is pH dependent, and the optimum pH range for a solution. Table 5 summarizes the stability of prepared solutions. Additionally, Table 6 summarizes stability of prepared solutions at 40° C./75% Relative Humidity and at 70° C., with and without pH adjustment with glycine. We found that as additional glycine HCl is added to solution, the amount of degradant at RRT 0.79 formed is greatly reduced and confirms the stability of the formulation with respect. . . of glycine. See Tables 5 and 6.

TABLE 4

Stability data of MNTX 12 mg/vial, 0.28 mg/vial CaEDTA and 0.65% Sodium Chloride
pH(5.6) at 70° C.

Initial	RRT	RRT	RRT	RRT	RRT	RRT	RRT

RRT RRT RRT RRT RRT RRT
(mg) 0.38. . .
DETD
TABLE 5

Stability of MNTX formulation 20 mg/ml, 0.4 mg/ml CaEDTA, 0.65% Sodium Chloride with pH adjusted with Glycine HCl

	Initial	RRT	RRT	RRT	RRT	RRT	RRT	RRT	RRT
	RRT	RRT	RRT	RRT	RRT				
	(mg).	.	.	1.77	1.89	1.96	2.01	2.26	Total
Specifications	NA	0.2	0.5	0.5	0.5	0.15	0.15	0.5	0.15
0.5	0.2	0.2	0.2	0.5	NA				
pH 3 at 40° C./75% Relative Humidity									
Time and Days									
Initial	19.8	BRL	BRL	BRL	BRL	BRL	BRL	BRL	0.11
BRL	BRL	BRL.	.	.	BRL	BRL	BRL	BRL	BRL 0.12
30	20.1	BRL	BRL	BRL	BRL	BRL	BRL	BRL	0.12
BRL	BRL	BRL	BRL	BRL	0.12				
pH 3.5 at 40° C./75% Relative Humidity									
Initial	19.9	BRL	BRL	BRL	BRL	BRL	BRL	BRL	0.12
BRL	BRL	BRL	BRL	BRL.	.	.	BRL	BRL	BRL BRL BRL 0.11
30	20.1	BRL	BRL	BRL	BRL	BRL	BRL	BRL	0.12
BRL	BRL	BRL	BRL	BRL	0.12				
pH 4 at 40° C./75% Relative Humidity									
Initial	20.0	BRL	BRL	BRL	BRL	BRL	BRL	BRL	0.12
BRL	BRL	BRL	BRL	BRL.	.	.			

DETD
TABLE 6

Stability of MNTX formulation 20 mg/ml, 0.4 mg/ml CaEDTA, 0.65% Sodium Chloride with pH adjusted with Glycine HCl

	Initial	RRT	RRT	RRT	RRT	RRT	RRT	RRT
	RRT	RRT	RRT	RRT	RRT			
	(mg).	.	.	1.77	1.89	1.96	2.01	2.26	Total
Specifications	NA	0.2	0.5	0.5	0.5	0.15	0.15	0.5
0.15	0.5	0.2	0.2	0.2	0.5	NA			
pH 3 at 70° C.									
Time and Days									
Initial	19.8	BRL	BRL	BRL	BRL	BRL	BRL	BRL	
0.11	BRL	BRL	BRL	BRL	BRL.	.	.	BRL	BRL BRL 0.06
0.12									
	(99)								
14		BRL	BRL	0.07	0.05	BRL	BRL	BRL	
0.11	BRL	BRL	BRL	BRL	0.09	0.32			
pH 3.5 at 70° C.									
Initial	19.9	BRL	BRL	BRL	BRL	BRL	BRL	BRL	
0.12	BRL	BRL	BRL	BRL	BRL	0.12			
	(100).	.	.	BRL	BRL	BRL	BRL	0.11	0.38
12	20.2	BRL	BRL	0.06	0.15	BRL	BRL	BRL	

0.11 0.06 BRL BRL BRL 0.18 0.56
pH 4 at 70° C.
Initial 20.0 BRL BRL BRL BRL BRL BRL BRL
0.12 BRL BRL BRL BRL BRL 0.12
(100). . .

DETD Preparation of a pH Adjusted, Improved Room Temperature Formulation. Listed Below, in Table 7 and Table 8, are developed formulations containing glycine HCl, including a pH adjustment step in the process, where the range of pH is 3.4-3.6 with a target pH 3.5. While not being bound by theory, this is based on the idea that while pH 3.0 is stable, the amount of irritation and sting at the site of injection would be undesirable. Furthermore, at pH 4.0, RRT 0.79 degradant begins to form. Glycine HCl is commonly used in subcutaneous formulations for pH adjustment, and has less propensity to cause site of injection stinging as results with use of citrate buffer. When glycine HCl is used to adjust the pH of formulations containing methylnaltrexone, controlling degradation is also evident. A solution containing methylnaltrexone including both CaEDTA and 0.3 mg/mL glycine HCl where the pH is adjusted to 3.4-3.6 will inhibit the formation of RRT 1.55 and greatly reduce the formation of degradants RRT 0.67. . . and RRT 0.79. A room temperature liquid formulation consisting of methylnaltrexone, CaEDTA, 0.65% NaCl, 0.3 mg/mL glycine HCl with a pH to 3.5 may be developed as either a subcutaneous administration or intravenous administration formulation.

DETD . . . of Such Improved Formulations Comprises Use of the Following exemplary components:

Active	Methylnaltrexone bromide	(5 to 40 mgs)
Chelating agent	Calcium EDTA	(0.05 to 1.5)
Isotonic Delivery Vehicle	0.65% Normal Saline	(0.5 to 1.75 mL)
Stabilizer	glycine HCl	0.3 mg/mL pH 3.4-3.6

DETD QS to Final Volume

TABLE 7

Formulation INGREDIENTS	12 Mg/VIAL.sup.A	16 Mg/VIAL.sup.A	
Methylnaltrexone bromide	12 mg	16 mg	20 mg/mL
Calcium EDTA disodium dihydrate, NF	0.24 mg	0.0.32 mg	0.4 mg/mL
Sodium Chloride	3.9 mg	5.20 mg	6.5 mg/mL
Glycine HCL	0.18 mg pH 3.5	0.0.24 mg pH 3.5	0.3 mg/mL pH 3.5
Water for Injection, USP	QS to 0.6	QS to 0.8	

.sup.A3 mL West flint glass vial with 13 mm West 4432/50. . .

DETD . . . mgs of methylnaltrexone bromide and 3.9 mg sodium chloride were dissolved in water for injection; then 0.24 mg of calcium EDTA added and dissolved the final solution brought to a final fill volume of 0.6 mL. The pH was adjusted with

Glycine HCl to between 3.4-3.6, optimally pH 3.5. Resulting solution was prepared, and filtered through 0.45 and 0.22 micron PVDF filters. Resulting solution was filled into clear glass vials under low oxygen conditions. Any suitable containers, including vials, ampoules, syringes or auto-dispensers may. . .

DETD . . . obtain the same concentrations. See Table 7.

TABLE 8

Formulation INGREDIENTS	12 Mg/VIAL.sup.A	16 Mg/VIAL.sup.A	
Methylnaltrexone bromide	12 mg	16 mg	10 mg/mL
Calcium EDTA disodium dihydrate, NF	0.24 mg	0.0.32 mg	0.2 mg/mL
Sodium Chloride	3.9 mg	5.20 mg	3.25 mg/mL
Glycine HCL	0.18 mg	0.0.24 mg	0.15 mg/mL
	pH 3.5	pH 3.5	
pH 3.5			
Water for Injection, USP	QS to 1.2	QS to 1.6	

.sup.A3 mL West flint glass vial with 13 mm West 4432/50. . .

DETD . . . mgs of methylnaltrexone bromide and 3.9 mg sodium chloride were dissolved in water for injection; then 0.24 mg of calcium EDTA added and dissolved and the final solution brought to a final fill volume of 1.2 mL. The pH was adjusted with Glycine HCl to between 3.4-3.6, optimally pH 3.5. Resulting solution was prepared, and filtered through 0.45 and 0.22 micron PVDF filters. Resulting solution was filled into clear glass vials under low oxygen conditions. Any suitable containers, including vials, ampoules, syringes or auto-dispensers may. . .

DETD Evaluation of phosphate buffers solution stability. We have also assessed different buffers to determine compatibility and whether various conditions would convey further stability to methylnaltrexone. . . and Table 10 show results (HPLC Method A) of total degradant formation over time in methylnaltrexone solutions prepared in phosphate solution (Table 9), and glycine solution (Table 10). We found at pH 7, glycine provides better stability characteristics to samples than phosphate.

TABLE 9

Stability of MNTX in pH 7, 0.02M Phosphate* Solution

Condition	Elapsed Time	Strength (mg/ml)	% Initial	Total Impurities (% Total Area)	pH of Formulation	Appearance and Description
Room Temperature	0 time	0.988	100	0.025	7.09	Clear, colorless solution
	1 day	0.988	100	0.134	7.12	Clear, colorless

	solution						
	2 days	0.996	100.8	0.262	7.11		Clear, colorless
	solution						
	6 days	0.999	101.1	0.786	7.14		Clear, colorless
	solution						
	9 days	0.999	101.1	1.25	7.14		Clear, colorless
	solution						
	14 days	0.988	100.0	1.561	7.14		Clear, colorless
	solution						
	21 days	0.971	98.3	2.07	7.09		Clear, colorless
	solution						
40° C.	0 time	1.092	100	0.06	7.08	Clear,	
	solution						
	1 day	1.069	97.9	0.471	7.15		Clear, colorless
	solution						
	2 days	1.066	97.6	1.771	7.36		Clear, colorless
	solution						
	6 days	1.043	95.5	4.297	7.12		Clear, colorless
	solution						
	9 days	1.027	94.0	5.648	7.11		Clear, colorless
	solution						
	14 days	1.006	92.1	8.3	7.09		Clear, very slightly yellow sol.
	21 days	0.973	89.1	11.613	7.08		Clear, very slightly yellow sol.
60° C.	0 time	1.092	100	0.06	7.08	Clear,	
	solution						
	1 day	1.028	94.1	6.109	7.12		Clear, colorless

	solution					
		2 days	0.991	90.8	10.291	7.17	Clear, colorless
	solution					
		6 days	0.877	80.3	22.512	7.08	Clear, colorless
	solution					
		9 days	0.806	73.8	28.351	7.06	Clear, yellow
	solution					
		14 days	0.726	66.5	35.59	7.04	Clear, yellow
	solution					
		21 days	0.745	68.2	42.23	6.94	Clear, yellow
	solution					

*Phosphate Buffer: KH.sub.2PO.sub.4 and Na.sub.2HPO.sub.4
DETD
TABLE 10

Stability of MNTX in pH 7, 0.02M Glycine* Solution

Condition	Elapsed Time	Strength (mg/ml)	% Initial	Total Impurities (% Total Area)	pH of Formulation	Appearance and Description
Room Temperature	0 time	0.993	100	0.11	7.06	Slightly yellowish, clear
	solution					
		1 day	0.993	100	0.076	6.91	Clear, colorless
	solution					
		2 days	0.994	100.1	0.14	7.11	Clear, colorless
	solution					
		6 days	0.987	99.4	0.302	7.37	Slight precipitate on
		9 days	1.005	101.2	0.425	7.99	the bottom Slightly hazy on
. . .	bottom						
		14 days	0.998	100.5	0.32	7.21	Slightly

							hazy on the bottom
	21 days	0.989	99.6	0.62	7.16		Clear, colorless solution
40° C.	0 time	1.051	100	0.097	7.15	Clear,	
	1 day	1.04	99.0	0.403	7.53		Clear, colorless solution
	2 days	1.039	98.9	0.379	7.69		Clear, colorless solution
	6 days	1.043	99.2	0.468	7.50		Clear, colorless solution
	9 days	1.039	98.9	0.669	7.16		Clear, colorless solution
	14 days	1.036	98.6	0.74	7.55		Clear, colorless solution
	21 days	1.01	96.1	0.975	7.26		Clear, colorless solution
60° C.	0 time	1.051	100	0.097	7.15	Clear,	
	1 day	1.032	98.2	1.046	7.20		Clear, colorless solution
	2 days	1.032	98.2	1.757	7.27		Clear, colorless solution
	6 days	1.002	95.3	4.043	6.98		Clear, colorless solution
	9 days	0.977	93.0	5.294	6.95		Clear, light yellow solution
	14 days	0.959	91.2	6.51	6.94		Clear, light yellow solution

21 days	0.937	89.2	9.122	6.37	Clear, light yellow solution

*Glycine Buffer: Glycine and NaOH

DETD Preparation of a Methylnaltrexone Formulation Comprising Sodium EDTA and citrate buffer. Methylnaltrexone formulations consisting of methylnaltrexone, sodium EDTA, and sodium chloride in citrate buffer have been described (see US Patent Application Publication US2004/0266806A1, published Dec. 30, 2004). We. . .

DETD Formulations containing 20 mg/mL methylnaltrexone bromide in either A-0.7 mg/mL NaEDTA/pH 3.5 adjusted with citrate buffer; and B-0.4 mg/mL CaEDTA/0.65% NaCl/pH 3.5 adjusted with glycine buffer were prepared. Each of the formulations were assessed over time for presence of degradant formation,. . .

DETD Under aggressive stability conditions, solutions containing sodium EDTA, even high levels of sodium EDTA, the 0.67 and the 0.79 degradant begin to increase. It is believed the formulations and methods provided herein for production. . . of 20 mg/mL methylnaltrexone formulation

TABLE 11A

Stability data for liquid formulation containing 20 mg/ml MNTX, 0.7 mg/ml NaEDTA 0.4% Sodium Chloride and pH 3.5 adjusted with Citric buffer (HPLC Method B)

	RRT	RRT	RRT	RRT	RRT	RRT	RRT	RRT
Initial (mg). . .	BRL		0.14		BRL		0.30	1.21

Table 11B

Stability data for liquid formulation 20 mg/ml MNTX, 0.4 mg/ml CaEDTA and 0.65% Sodium Chloride with pH 3.5 adjusted with Glycine Hydrochloride (HPLC Method B)

	RRT	RRT	RRT	RRT	RRT	RRT	RRT	RRT
Initial (mg). . .	1.96	RRT 2.01		RRT 2.26		Total		

Specifications	NA	0.2	0.5	0.5	0.5	0.15	0.15	0.5	0.15	0.5	0.2	0.2	0.2	0.5	NA

pH 3.5 at Room Temperature

Time and Days															
Initial	20.2	BRL	BRL	BRL	BRL	BRL	BRL	BRL	0.12	BRL	BRL	BRL	BRL. . .	BRL	BRL
30	19.8	BRL	BRL	BRL	BRL	BRL	BRL	BRL	0.11	BRL	BRL	BRL	BRL	0.11	

pH 3.5 at 40° C./75% Relative Humidity

Initial	19.9	BRL	BRL	BRL	BRL	BRL	BRL	BRL	0.12	BRL	BRL	BRL	BRL. . .	BRL	BRL
30	20.1	BRL	BRL	BRL	BRL	BRL	BRL	BRL	0.11	BRL	BRL	BRL	BRL	0.12	

pH 3.5 at 70° C.

Initial 19.9 BRL BRL BRL BRL BRL BRL BRL
0.12 BRL BRL BRL BRL BRL 0.12
5. . . BRL 0.11 0.06 BRL BRL BRL 0.18
0.56

Table 11C-1
Stability Data for Methylnaltrexone Bromide, 20 mg/mL Injection,
CaEDTA Formulation
Storage Time Description Reconstituted
Solution Strength pH
Edetate Calcium Disodium Content

Specification Clear solution, colorless to
pale yellow, 90.0-110.0% LC 3.0-5.0 0.36-0.44 mg/mL
essentially free of visible particulates
Method HPLC Method A
L28228-147 USP <791>. . . tested;
NMT = Not more than;
RRT = Relative retention time;
FIO = For information only.
.sup.aOnly one determination for pH was performed (n = 1).
.sup.bProcess impurities found in the drug substance. Tested for information
.sup.cThe unspecified degradant at RRT. . .
DETD . . . Comparisons of 5 mg/mL (12 mg/vial or 24 mg/vial)
methylnaltrexone
formulation

Table 12A-1
Stability Data for Methylnaltrexone Bromide, 5 mg/mL (12 mg/ vial)
IV Solution for Injection, CaEDTA Formulation
Storage Time Strength
pH Edetate Calcium
Disodium Content

Specification 90.0-110.0% LC
3.0-5.0 0.09 0.11 g/mL
Method HPLC Method A
USP <791> L34449-051
Initial 98.9, 98.3, 98.8
3.6,. . . Exposed 103.1 3.7, 3.7
0.091
Packaged 99.4
3.6, 3.6 0.095

Table 12A-2
Stability Data for Methylnaltrexone Bromide, 5 mg/mL (12 mg/ vial)
IV Solution for Injection, CaEDTA Formulation,
Degradation/Impurities
Ring
7-Di- Con- Nal- 2,2'-
O- Hofmann Any Unspecified Total
RRT RRT hydroxy S-. . . BRL BRL BRL
BRL BRL BRL 0.07 BRL BRL BRL
BRL

Table 12B-1

Stability Data for Methylnaltrexone Bromide, 5 mg/mL (24 mgvial)
IV Solution for Injection, CaEDTA Terminally Sterilized

Storage Time			Strength
pH	Edetate Calcium Disodium Content		
Specification			90.0–110.0% LC
3.0–5.0	0.09 0.11 g/mL		
Method			HPLC Method A
USP <791>	L34449-051		
Initial			99.4, 99.7, 99.7
3.6, 3.7	0.093		
25°. . .	Study	Exposed	100.3
3.7, 3.6	0.095		
		Packaged	99.6
3.7, 3.7	0.090		

Table 12B-2
Stability Data for Methylnaltrexone Bromide, 5 mg/mL (24 mgvial)
IV Solution for Injection, CaEDTA Terminally Sterilized

	Degradation/Impurities							
			Any					
			7-Di-		Ring	Nal-		
O-	Hofmann		Unspecified		Total			
	RRT	RRT	hydroxy	S-	Con-. . .	BRL	BRL	BRL
BRL	BRL	BRL	0.07	BRL	BRL	BRL		
BRL								
aged								

Table 12C-1
Stability Data for Methylnaltrexone Bromide, 5 mg/mL (24 mgvial)
IV Solution for Injection, CaEDTA Formulation

Storage Time			Strength
pH	Edetate Calcium Disodium Content		
Specification			90.0–110.0% LC
3.0–5.0	0.09 0.11 g/mL		
Method			HPLC Method A
USP <791>	L34449-051		
Initial			99.8, 99.3, 99.2
3.6,. . .	Study	Exposed	102.6
3.5, 3.6	0.092		
		Packaged	99.8
3.6, 3.6	0.095		

Table 12C-2
Stability Data for Methylnaltrexone Bromide, 5 mg/mL (24 mgvial)
IV Solution for Injection, CaEDTA Formulation,

	Degradation/Impurities							
					Ring			
			7-Di-		Con-	Nal-		
O-	Hofmann		Any Unspecified		Total			
	RRT	RRT	hydroxy	S-	trac-. . .	BRL		
BRL	BRL	BRL	BRL	BRL	0.06	BRL	BRL	
BRL		BRL						

Table 12D-1
Stability Data for Methylnaltrexone Bromide, 5 mg/mL (24 mgvial)
IV Solution for Injection, CaEDTA Formulation (Terminally Sterilized)
(HPLC Method A)

Storage Time		Strength	
pH	Edetate Calcium Disodium Content		
Specification		90.0-110.0% LC	
3.0-5.0	0.09 0.11 g/mL		
Method		L28228-147	
USP <791>	L34449-051		
Initial		99.7, 99.8, 98.2	
3.5, 3.5	0.095		
. . . Exposed	103.1	3.7, 3.6	0.093
	Packaged	100.1	
3.6, 3.6	0.092		

Table 12D-2
Stability Data for Methylnaltrexone Bromide, 5 mg/mL (24 mgvial) IV Solution for Injection,
CaEDTA Formulation (Terminally Sterilized),
Degradation/Impurities

				Ring-Con-		
	7-Di-				Nal-	
O-	Hofmann		Any	Unspecified		Total
	RRT	RRT	hydroxy	S-. . .		

DETD . . . in vial closures for their compatibility with methylnaltrexone solutions, and determined whether any had effects on formation of degradants in solution.

DETD A room temperature methylnaltrexone formulation 20 mg/mL subcutaneous solution for injection, CaEDTA formulation consists of 20 mg/mL methylnaltrexone bromide, 0.4 mg/mL edetate calcium disodium (CaEDTA), 0.3 mg/mL glycine hydrochloride and 0.65% sodium chloride in water for injection. The product, which is stable at room. . .

DETD . . . formulation for subcutaneous administration was prepared as summarized in Tables 17A, 17B, and 17C below:

TABLE 17A

Methylnaltrexone 20 mg/mL Subcutaneous Solution for Injection, SC Commercial

Formulation	Strength	20 mg/mL
	Type	Liquid Solution
Container/Closure	Vial	3 mL
	Stopper	13 mm
mg/vial	Methylnaltrexone	12 mg
	CaEDTA	0.32
	Glycine HCl	0.24
	NaCl	5.20
	Overage	33%. . .

DETD

TABLE 17B

Methylnaltrexone 20 mg/mL Subcutaneous Solution for Injection, Room Temperature

MNTX	20 mg/mL
CaEDTA.sup.#	0.40 mg/mL
Glycine HCL	0.30 mg/mL
NaCl	6.5 mg/mL
Osmolarity (mOsm/Kg)	286
pH	3-5
Volume of injection (mL)	0.6

DETD

TABLE 17C

Methylnaltrexone 20 mg/mL Subcutaneous Solution for Injection, Quantitative Composition

Methylnaltrexone 20 mg/mL Subcutaneous Solution for Injection, CaEDTA Formulation, Batch Size: 5000 mL

Ingredient	% WT/WT	Input/ Dosage Unit Input	Unit
Naltrexone Methobromide	1.985	16	mg
Calcium EDTA, USP	0.040	0.32	mg
Sodium Chloride, USP	0.644	5.2	mg
Glycine Hydrochloride	0.030	0.24	mg
Water for Injection, USP	NA. . .		

DETD . . . syringe is described below in Table 18.

TABLE 18

Pre-filled Syringe

	Concentration/Limits	
Active Ingredients		
Methylnaltrexone Bromide	20	mg/mL
Excipients		
Calcium Disodium Edetate	0.4	mg/mL
Glycine Hydrochloride	0.3	mg/mL
Sodium Chloride	6.5	mg/mL
Water for Injection (WFI)	Ad 1.0	mL

Primary Packaging Materials Type. . .

DETD . . . week later, during period 2, Group 1 (SAN 1-4) received 0.15 mg/kg methylnaltrexone subcutaneously in saline containing 0.5 mg/vial Na. EDTA and 0.6 mM Citrate (Batch 2) and Group 2 (SAN 5-8) received 0.15 mg/kg methylnaltrexone subcutaneously in saline containing 0.5 mg/vial Ca. EDTA (Batch 3). Blood samples were drawn at 0 (predose), 0.0833, 0.167, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8 and. . .

DETD . . . calibrated pump.

TABLE 20A

Methylnaltrexone IV formulation for 12 mg/Vial

Ingredient	% WT/WT	Input/ Dosage Unit Input	Unit
Naltrexone Methobromide	0.496	25.2	mg
Calcium EDTA, USP	0.0099	0.504	mg
Sodium Chloride, USP	0.833	42.336	mg
Glycine Hydrochloride	0.0099	0.504	mg
Water for Injection, USP	NA	QS to 2.54	mL

Fomulation	Strength	IV 5 mg/mL	
	Type	Liquid Solution	
Container/Closure	Vial	10 mL	10 mL
	Stopper	20 mm	20 mm
mg/vial	Methylnaltrexone	12 mg	24 mg
	CaEDTA	0.24 mg	0.48 mg

. . .
DETD
TABLE 20B

Methylnaltrexone IV formulation for 24 mg/Vial

DESCRIPTION	AMT. NEEDED PER UNIT	
Methylnaltrexone	25.2	mg
Calcium EDTA, USP	0.504	mg
Sodium Chloride, USP	42.336	mg
Glycine Hydrochloride	0.504	mg
Water for Injection, USP.sup.a	5.08.sup.c	g
Hydrochloric Acid, NF.sup.b	As needed	NA

Sodium. . . XKD484
20 mm, Aluminum seal with Flip-top

Ingredient	% WT/WT	Input/ Dosage Unit Input	Unit
Methylnaltrexone	0.496	25.2	mg
Calcium EDTA, USP	0.0099	0.504	mg
Sodium Chloride, USP	0.833	42.336	mg
Glycine Hydrochloride	0.0099	0.504	mg
Water for Injection, USP	NA. . .		

DETD . . . 5%

Fill volume	2.52	5.04	2.52	5.04
Reconstitution volume	8.0 mL of saline	5.0 mL of saline solution	8.0 mL of saline	5.0 mL of saline

Withdrawal amount	Spike solution full contents of vial	Spike solution full contents of vial	Withdraw solution 10.0 mL via syringe	Withdraw solution 10.0 mL via syringe

CLM What is claimed is:
. . . from at least methylnaltrexone or a pharmaceutically acceptable salt thereof, a calcium salt, and a chelating agent in an aqueous solution.

CLM What is claimed is:
3. The pharmaceutical composition of claim 2 wherein the calcium salt chelating agent is selected from the group calcium ethylenediaminetetraacetic acid (EDTA), calcium diethylenetriaminepentaacetic acid (DTPA), calcium hydroxyethylenediaminetriacetic acid (HEDTA), calcium ethylene glycol-bis-(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), calcium nitrilotriacetic acid (NTA), calcium citrate, and. . .

CLM What is claimed is:
8. The pharmaceutical composition of claim 3, wherein the calcium salt chelating agent is calcium ethylenediaminetriacetic acid (EDTA), or calcium ethylene glycol-bis-(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), or calcium salt derivatives thereof.

CLM What is claimed is:
9. The pharmaceutical composition of claim 1, wherein the solution has a pH of between 2.5 and pH 6.

CLM What is claimed is:
10. The pharmaceutical composition of claim 9, wherein the pH is between about pH 3 and about pH 4.

CLM What is claimed is:
. . . least methylnaltrexone or a pharmaceutically acceptable salt thereof, a calcium salt chelating agent, and a stabilizing agent in an aqueous solution, wherein the solution has a pH of between 2.5 and 6.0.

CLM What is claimed is:
13. The pharmaceutical composition of claim 12, wherein the calcium salt chelating agent is selected from the group calcium ethylenediaminetetraacetic acid (EDTA), calcium diethylenetriaminepentaacetic acid (DTPA), calcium hydroxyethylenediaminetriacetic acid (HEDTA), calcium ethylene glycol-bis-(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), calcium nitrilotriacetic acid (NTA), calcium citrate, and. . .

CLM What is claimed is:
18. The pharmaceutical composition of claim 12, wherein the aqueous solution comprises water for injection.

CLM What is claimed is:
19. The pharmaceutical composition of claim 13, wherein the calcium salt chelating agent is calcium ethylenediaminetriacetic acid (EDTA) or calcium ethylene glycol-bis-(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), or calcium salt derivatives thereof.

CLM What is claimed is:
22. The pharmaceutical composition according to claim 12, wherein an effective amount of glycine maintains the pH at about 3.0 to about 4.0.

CLM What is claimed is:
23. The pharmaceutical composition according to claim 22 wherein the pH is about 3.5.

CLM What is claimed is:
. . . wherein the container has a space sufficient for introduction of a volume of aqueous solvent sufficient to form a diluted solution of the dose concentrate.

CLM What is claimed is:
. . . wherein the container has a space sufficient for introduction of a volume of aqueous solvent sufficient to form a diluted solution of the dose concentrate.

CLM What is claimed is:
30. A pharmaceutical composition comprising methylnaltrexone or a pharmaceutically acceptable salt thereof, calcium EDTA or a calcium salt derivative thereof, and glycine in an aqueous carrier.

CLM What is claimed is:
. . . claim 30, characterized by one or more of (a) through (d): a. the methylnaltrexone is methylnaltrexone bromide; b. the calcium EDTA is calcium EDTA disodium; c. the glycine is glycine hydrochloride; and d. the aqueous carrier is isotonic sodium chloride.

CLM What is claimed is:
32. The pharmaceutical composition of claim 31, wherein the composition has a pH of between about pH 3 and about pH 4.

CLM What is claimed is:
34. The pharmaceutical composition of claim 33, wherein the composition has a pH between about pH 3.4 and about pH 3.6.

CLM What is claimed is:
. . . of methylnaltrexone, or a pharmaceutically acceptable salt thereof, a calcium salt chelating agent, and a stabilizing agent in an aqueous solution, wherein a concentration of degradation products in the composition following six months of room temperature storage conditions is characterized by. . .

CLM What is claimed is:
. . . of methylnaltrexone or a pharmaceutically acceptable salt thereof, a calcium salt chelating agent, and a stabilizing agent in an aqueous solution, wherein a concentration of degradation products in the composition following six months of room temperature storage conditions is characterized by. . .

CLM What is claimed is:
39. A method of preparing a methylnaltrexone formulation for parenteral

administration, the method comprising the steps of: preparing a solution comprising methylnaltrexone or a pharmaceutically acceptable salt thereof, an isotonic agent and a calcium salt chelating agent; and sterilizing the resulting solution and distributing to one or more sealed containers.

CLM What is claimed is:
40. The method of claim 39, wherein the calcium salt chelating agent is selected from the group calcium ethylenediaminetetraacetic acid (EDTA), calcium diethylenetriaminepentaacetic acid (DTPA), calcium hydroxyethylenediaminetriacetic acid (HEDTA), calcium ethylene glycol-bis-(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), calcium nitrilotriacetic acid (NTA), calcium citrate, and. . .

CLM What is claimed is:
42. The method of claim 39, wherein the solution comprises an isotonic agent.

CLM What is claimed is:
45. The method of claim 39, wherein the solution comprises water for injection.

CLM What is claimed is:
46. The method of claim 39, wherein the calcium salt chelating agent is calcium ethylenediaminetriacetic acid (EDTA) or calcium ethylene glycol-bis-(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA) or a calcium salt derivative thereof.

CLM What is claimed is:
47. The method of claim 39 wherein the solution comprises a stabilizing agent.

CLM What is claimed is:
49. The method of claim 48, wherein an effective amount of glycine maintains pH at about 3.0 to about 4.0.

CLM What is claimed is:
50. The method of claim 49, wherein the pH is about 3.5.

CLM What is claimed is:
51. A method of preparing a methylnaltrexone formulation, the method comprising the steps of: preparing a solution comprising methylnaltrexone or a pharmaceutically acceptable salt thereof, an isotonic agent, a calcium salt chelating agent and a stabilizing agent; adjusting the pH of the solution to between pH 2.0 and pH 6.0; and sterilizing the resulting solution and distributing to one or more sealed containers.

CLM What is claimed is:
52. The method of claim 51, wherein the calcium salt chelating agent is selected from the group calcium ethylenediaminetetraacetic acid (EDTA), calcium diethylenetriaminepentaacetic acid (DTPA), calcium hydroxyethylenediaminetriacetic acid (HEDTA), calcium ethylene glycol-bis-(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), calcium nitrilotriacetic acid (NTA), calcium citrate, and. . .

CLM What is claimed is:
56. The method of claim 51, wherein the aqueous solution comprises water for injection.

CLM What is claimed is:
57. The method of claim 52, wherein the calcium salt chelating agent is calcium ethylenediaminetriacetic acid (EDTA) or calcium ethylene glycol-bis-(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), or a calcium salt derivative thereof.

CLM What is claimed is:
60. The method of claim 51, wherein an effective amount of glycine maintains pH at about 3.0 to about 4.0.

CLM What is claimed is:
61. The method of claim 60, wherein the pH is about 3.5.

IT 16590-41-3 916045-21-1 1005410-32-1 1005410-34-3 1005410-37-6 1005410-39-8 1005410-42-3 1005410-45-6 1005410-47-8 1005476-90-3
(formulations for parenteral delivery of compds. and uses thereof)
IT 50-21-5, Lactic acid, biological studies 50-70-4, Sorbitol, biological studies 50-99-7, Dextrose, biological studies 56-40-6, Glycine, biological studies 56-81-5, Glycerol, biological studies 62-33-9 63-42-3, Lactose 65-85-0, Benzoic acid, biological studies 69-65-8, Mannitol 77-92-9, Citric acid, biological studies 79-14-1, Glycolic acid, biological studies 110-16-7, Maleic acid, biological studies 2531-75-1, Calcium diethylenetriaminepentaacetic acid 6000-43-7, Glycine hydrochloride 6915-15-7, Malic acid 7440-70-2D, Calcium, salts 7647-14-5, Sodium chloride, biological studies 7693-13-2, Calcium citrate 8022-63-7, Lactated ringer's injection 14981-08-9 33242-13-6 73232-52-7, Methylnaltrexone
(formulations for parenteral delivery of compds. and uses thereof)

L9 ANSWER 4 OF 15 USPATFULL on STN

ACCESSION NUMBER:	2008:66450 USPATFULL
TITLE:	1-[[1-[(2-Amino-6-methyl-4-pyridinyl)methyl]-4-fluoro-4-piperidinyl]carbonyl]-4-[2-(2-pyridinyl)-3H-imidazo[4,5-b]pyridin-3-yl]piperidine and Methods of Use Thereof
INVENTOR(S):	de Lera Ruiz, Manuel, Branchburg, NJ, UNITED STATES Aslanian, Robert G., Rockaway, NJ, UNITED STATES Berlin, Michael Y., Flemington, NJ, UNITED STATES McCormick, Kevin D., Basking Ridge, NJ, UNITED STATES Celly, Chander S., Colonia, NJ, UNITED STATES
PATENT ASSIGNEE(S):	Schering Corporation (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20080058370	A1	20080306
APPLICATION INFO.:	US 2007-837248	A1	20070810 (11)
RELATED APPLN. INFO.:	Division of Ser. No. US 2006-523489, filed on 19 Sep 2006, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-718673P	20050920 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	SCHERING-PLOUGH CORPORATION, PATENT DEPARTMENT (K-6-1,

1990), 2000 GALLOPING HILL ROAD, KENILWORTH, NJ, 07033-0530, US
NUMBER OF CLAIMS: 41
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 1314
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the. . . amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example. . .

DETD . . . the combination can be administered individually or together in any conventional dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc. In one embodiment, the dose of the other therapeutic agent ranges from about 1 mg to. . .

DETD LiAlH.sub.4 (10.0 g, 0.264 mol, 1.24 eq) was added portionwise to a solution of methyl-2-chloro-6-methylpyridine-4-carboxylate 1 (39.62 g, 0.213 mol) in dry Tf (800 mL) at room temperature with stirring over a period. . .

DETD Di-tert-butyl dicarbonate (105.75 g, 0.485 mol, 4.33 eq) was added to a stirred solution of 3 (15.51 g, 0.112 mol) in tert-butyl alcohol (500 mL) at room temperature. The resulting mixture was heated at. . . to give the diprotected aminoalcohol (38.25 g) as a yellow solid. 25% aqueous NaOH (150 mL) was added to a solution of the above material in MeOH (500 mL) over a period of 10 min. The resulting mixture was stirred for. . .

DETD Dess-Martin periodinane (50.0 g, 0.118 mol, 1.34 eq) was portlonwise added to a solution of 4 (21.0 g, 0.088 mol) in dichloromethanepyridine 10:1 (1.1 L). The resulting solution was stirred at room temperature for 2 h and then water (700 mL) was added. The mixture was stirred for. . .

DETD NaBH(OAc).sub.3 (57.8 g, 0.274 mol, 1.6 eq) was added to a solution of piperidine 6 (69.97 g, 0.171 mol, prepared using the method described in Example 2, below) and 5 (52.6 g,. . .

DETD TFA (900 mL) was added to a solution of 7 (93.38 g, 0.149 mol) in dichloromethane (2.7 L). The resulting solution was stirred under a N.sub.2 atmosphere for 26 h, then cooled to 0° C. and carefully basified with 15% aqueous ammonia solution. The layers were separated and the aqueous layer extracted with dichloromethane (1+1.5 L). The combined organic phase was dried and. . .

DETD A solution of compound 8 (100 g, 0.389 mol) in THF (400 mL) was added dropwise over 1 h to a solution of lithium diisopropylamide (233 mL, 2.0 M in THF/heptane/ethylbenzene, 0.466 mol) in THF (300 mL) at 0° C. The red-orange solution was stirred at 0° C. for 30 min, and then transferred by cannula to a pre-cooled (0° C.) solution of N-fluorobenzenesulfonimide (153 g, 0.485 mol) in dry THF (600 mL). The reaction mixture was stirred at 0° C. for. . . for 18 h. The total solvent volume was reduced to approximately one third, and EtOAc

(1 L) was added. The solution was washed successively with water, 0.1 N aqueous HCl, saturated aqueous NaHCO.sub.3, and brine. The organic layer was dried over. . .

DETD A solution of 9 (50 g, 0.181 mol) in THF (300 mL) and MeOH (200 mL) was treated with a solution of LiOH--H.sub.2O (9.2 g, 0.218 mol) in water (i00 mL) and then heated to 45° C. for 6 h. The. . .

DETD A solution of 15 (109 g, 0.41 mol) in dichloromethane:DMF 1:1 (500 mL) was treated with picolinic acid (61 g, 0.50 mol),. . .

DETD A solution of 16 (131 g, 0.36 mol) in acetic acid (200 mL) was heated at 120° C. overnight. The reaction mixture. . .

DETD A solution of 17 (95 g, 0.27 mol) in anhydrous CHCl.sub.3 (300 mL) was treated with iodotrimethylsilane (272 g, 1.36 mol) and. . .

DETD . . . 200 μL assay volume contained 1.0 nM [.sup.3H]N.sup.-α-methylhistamine, test compound, and 3 μg of membrane protein in 50 mM Tris-HCl, pH 7.4. Total binding was determined in the absence of compound and nonspecific binding in the presence of 10.sup.-5 M thioperamide.. . .

DETD . . . (1990). Frozen brains were thawed at room temperature and then disrupted in ten volumes (w:v) of ice-cold 50 mM Tris-HCl, pH 7.4, with a Polytron. Homogenates were centrifuged at 1000+g and supernatants then centrifuged at 50,000+g. Pellets from the second centrifugation. . .

DETD . . . 200 μL assay volume contained 1.0 nM [.sup.3H]N.sup.α-methylhlstamine, test compound, and 300 μg of membrane protein in 50 mM Tris-HCl, pH 7.4. Total binding was determined in the absence of compound and nonspecific binding in the presence of 10.sup.-5 M thioperamide.. . .

DETD . . . 3 mg/kg to fasted beagle dogs orally (PO) at 3 mg/g (0.4% MC formulation) and i.v. at 3 mg/g (captisol, pH 5.1 fornulation). Blood samples were taken at multiple time intervals for 48 hours post dosing. The blood samples were converted. . . was 1,7 mL/min/kg.

TABLE 2

Pharmacokinetic Parameters of the Compound of the Invention in Dogs after Oral (0.4% MC) and IV (captisol, pH 5.1) administration

Parameter (units)	Oral (N = 3)	IV (N = 3)
Dose (mg/kg)	3	3
AUC (0-∞)	18.9	32.8

. . .

DETD . . . then homogenized in 6 mL of chloroform:methanol (2:1), 4 mL water was added to the homogenized mixture and the resulting solution was vortexed, then centrifuged at 1000+g for 30 minutes. The chloroform layer was removed and dried under nitrogen to provide. . .

DETD . . . and at the end of the study (day 7), using jugular venipuncture and immediately placed into separated Vacutainer® tubes containing EDTA anticoagulant, and processed for plasma. The plasma was aspirated and divided into two aliquots (≥0.3 ml each) and each aliquot. . .

DETD A: Preparation of stock solution:

0.1, 1, 10, 100, 1000 ng/μL in 50:50 methanol:water (1000 in DMSO) for
standards.
1, 10, 100. . .
DETD B: Plasma standard curve and QC preparation: stock solution
spiked in matrix identical to samples.

Concentration of standard curve:
0, 1, 2.5, 5, 10, 25, 50,. . .
DETD C: Internal Standard Solution: 0.1 ng/μL of Compound Y in
acetonitrile.
DETD . . . 1) Pipette 40 μL of sample into a 1 mL 96-well plate.
2) Add 15 μL of internal standard solution to each well.
3) Gently vortex plate for 1 minute.
4) Centrifuge samples for 10 minutes (Eppendorf 5810. . .
IT 50-47-5, Desipramine 50-49-7, Imipramine 50-58-8, Phendimetrazine
tartrate 58-55-9, Theophylline, biological studies 90-84-6,
Diethylpropion 122-09-8, Phentermine 262-20-4, Phenoxathiin
299-45-6 302-79-4, Retinoic acid 458-24-2, Fenfluramine 465-65-6,
Naloxone 537-46-2, Methamphetamine 569-59-5, Phenindamine tartrate
634-03-7, Phendimetrazine 637-07-0, Clofibrate 3239-44-9,
Dexfenfluramine 6493-05-6, Pentoxifylline 11041-12-6, Cholestyramine
14721-66-5, Phytanic acid 14838-15-4, Phenylpropanolamine 16590-41-3,
Naltrexone 16617-07-5 17397-89-6, Cerulenin 18464-39-6,
Caroxazone 21489-20-3, Talsupram 22232-71-9, Mazindol 24526-64-5,
Nomifensine 25812-30-0, Gemfibrozil 29218-27-7, Toloxatone
30299-08-2, Clinofibrate 37762-06-4, Zaprinast 41859-67-0,
Bezafibrate 49562-28-9, Fenofibrate 52214-84-3, Ciprofibrate
54403-19-9 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine
55096-26-9, Nalmefene 60719-84-8, Amrinone 60762-57-4, Pirlindole
61413-54-5, Rolipram 61869-08-7, Paroxetine 63638-91-5, Brofaromine
68550-75-4, Cilostamide 69047-39-8, Binifibrate 71320-77-9,
Moclobemide 75330-75-5, Lovastatin 76990-56-2, Milacemide
77518-07-1, Amiflamine 78415-72-2, Milrinone 79617-96-2, Sertraline
79902-63-9, Simvastatin 81093-37-0, Pravastatin 91406-11-0, Esuprone
93957-54-1, Fluvastatin 94011-82-2, Bazinaprine 96206-92-7,
2-Methyl-6-(phenylethynyl)-pyridine 96609-16-4, Lifibrol 96829-58-2,
Orlistat 96829-59-3, Lipstatin 97240-79-4, Topiramate 103878-84-8,
Lazabemide 106650-56-0, Sibutramine 117854-28-1, Befol 121062-08-6,
Melanotan-II 127697-55-6, 4-[(E)-2-(5,6,7,8-Tetramethyl-2-naphthalenyl)-
1-propenyl]benzoic acid 134523-00-5, Atorvastatin 134564-82-2,
Befloxatone 139755-83-2, Sildenafil 145599-86-6, Cerivastatin
147511-69-1, Pitavastatin 153259-65-5, Cilomilast 163222-33-1,
Ezetimibe 168273-06-1, Rimonabant 169494-85-3, Leptin 175553-48-7,
Butabindide 180003-17-2, Oleoyl-estrone 287714-41-4, Rosuvastatin
329205-68-7, 3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]pyridine
444069-80-1, Axokine 879083-15-5, P 57
(codrug; preparation of 1-({1-[(2-amino-6-methyl-4-pyridinyl)methyl]-4-
fluoro-4-piperidinyl}carbonyl)-4-[2-(2-pyridinyl)-3H-imidazo[4,5-
b]pyridin-3-yl]piperidine as histamine H3 receptor modulator)

L9 ANSWER 5 OF 15 USPATFULL on STN DUPLICATE 1
ACCESSION NUMBER: 2007:76290 USPATFULL
TITLE: 1-[[1-[(2-Amino-6-methyl-4-pyridinyl)methyl]-4-fluoro-4-
piperidinyl]carbonyl]-4-[2-(2-pyridinyl)-3H-imidazo[4,5-
b]pyridin-3-yl]piperidine

INVENTOR(S): de Lera Ruiz, Manuel, Branchburg, NJ, UNITED STATES
Aslanian, Robert G., Rockaway, NJ, UNITED STATES
Berlin, Michael Y., Flemington, NJ, UNITED STATES
McCormick, Kevin D., Basking Ridge, NJ, UNITED STATES
Celly, Chander S., Colonia, NJ, UNITED STATES
PATENT ASSIGNEE(S): Schering Corporation (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070066644	A1	20070322
	US 7332604	B2	20080219
APPLICATION INFO.:	US 2006-523489	A1	20060919 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-718673P	20050920 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SCHERING-PLOUGH CORPORATION, PATENT DEPARTMENT (K-6-1, 1990), 2000 GALLOPING HILL ROAD, KENILWORTH, NJ, 07033-0530, US
NUMBER OF CLAIMS: 41
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 1316
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the. . . amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example. . .

DETD . . . the combination can be administered individually or together in any conventional dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc. In one embodiment, the dose of the other therapeutic agent ranges from about 1 mg to. . .

DETD LiAlH.sub.4 (10.0 g, 0.264 mol, 1.24 eq) was added portionwise to a solution of methyl-2-chloro-6-methylpyridine-4-carboxylate 1 (39.62 g, 0.213 mol) in dry THF (800 mL) at room temperature with stirring over a period. . .

DETD Di-tert-butyl dicarbonate (105.75 g, 0.485 mol, 4.33 eq) was added to a stirred solution of 3 (15.51 g, 0.112 mol) in tert-butyl alcohol (500 mL) at room temperature. The resulting mixture was heated at. . . to give the diprotected aminoalcohol (38.25 g) as a yellow solid. 25% aqueous NaOH (150 mL) was added to a solution of the above material in MeOH (500 mL) over a period of 10 min. The resulting mixture was stirred for. . .

DETD Dess-Martin periodinane (50.0 g, 0.118 mol, 1.34 eq) was portionwise added to a solution of 4 (21.0 g, 0.088 mol) in dichloromethane:pyridine 10:1 (1.1 L). The resulting solution was stirred at room temperature for 2 h and then water (700 mL) was added. The mixture was stirred for. . .

DETD NaBH(OAc).sub.3 (57.8 g, 0.274 mol, 1.6 eq) was added to a solution of piperidine 6 (69.97 g, 0.171 mol, prepared using the method described in Example 2, below) and 5 (52.6 g,. . .

DETD TFA (900 mL) was added to a solution of 7 (93.38 g, 0.149 mol) in dichloromethane (2.7 L). The resulting solution was stirred under a N.sub.2 atmosphere for 26 h, then cooled to 0° C. and carefully basified with 15% aqueous ammonia solution. The layers were separated and the aqueous layer extracted with dichloromethane (1+1.5 L). The combined organic phase was dried and. . .

DETD A solution of compound 8 (100 g, 0.389 mol) in THF (400 mL) was added dropwise over 1 h to a solution of lithium diisopropylamide (233 mL, 2.0 M in THF/heptane/ethylbenzene, 0.466 mol) in THF (300 mL) at 0° C. The red-orange solution was stirred at 0° C. for 30 min, and then transferred by cannula to a pre-cooled (0° C.) solution of N-fluorobenzenesulfonimide (153 g, 0.485 mol) in dry THF (600 mL). The reaction mixture was stirred at 0° C. for. . . for 18 h. The total solvent volume was reduced to approximately one third, and EtOAc (1 L) was added. The solution was washed successively with water, 0.1 N aqueous HCl, saturated aqueous NaHCO.sub.3, and brine. The organic layer was dried over. . .

DETD A solution of 9 (50 g, 0.181 mol) in THF (300 mL) and MeOH (200 mL) was treated with a solution of LiOH--H.sub.2O (9.2 g, 0.218 mol) in water (100 mL) and then heated to 45° C. for 6 h. The. . .

DETD A solution of 15 (109 g, 0.41 mol) in dichloromethane:DMF 1:1 (500 mL) was treated with picolinic acid (61 g, 0.50 mol),. . .

DETD A solution of 16 (131 g, 0.36 mol) in acetic acid (200 mL) was heated at 120° C. overnight. The reaction mixture. . .

DETD A solution of 17 (95 g, 0.27 mol) in anhydrous CHCl.sub.3 (300 mL) was treated with iodotrimethylsilane (272 g, 1.36 mol) and. . .

DETD . . . 200 μL assay volume contained 1.0 nM [.sup.3H]N.sup.α-methylhistamine, test compound, and 3 μg of membrane protein in 50 mM Tris.HCl, pH 7.4. Total binding was determined in the absence of compound and nonspecific binding in the presence of 10.sup.-5 M thioperamide.. . .

DETD . . . (1990). Frozen brains were thawed at room temperature and then disrupted in ten volumes (w:v) of ice-cold 50 mM Tris.HCl, pH 7.4, with a Polytron. Homogenates were centrifuged at 1000+g and supernatants then centrifuged at 50,000+g. Pellets from the second centrifugation. . .

DETD . . . 200 μL assay volume contained 1.0 nM [.sup.3H]N.sup.α-methylhistamine, test compound, and 300 μg of membrane protein in 50 mM Tris.HCl, pH 7.4. Total binding was determined in the absence of compound and nonspecific binding in the presence of 10.sup.-5 M thioperamide.. . .

DETD . . . 3 mg/kg to fasted beagle dogs orally (PO) at 3 mg/kg (0.4% MC formulation) and i.v. at 3 mg/kg (captisol, pH 5.1 formulation). Blood samples were taken at multiple time intervals for 48 hours post dosing. The blood samples were converted. . . was 1.7 mL/min/kg.

TABLE 2

Pharmacokinetic Parameters of the Compound of the Invention
in Dogs after Oral (0.4% MC) and IV (captisol, pH 5.1) administration

Parameter (units)	Oral (N = 3)	IV (N = 3)
Dose (mg/kg)	3	3
AUC (0-∞)	18.9	32.8

. . .
DETD . . . then homogenized in 6 mL of chloroform:methanol (2:1), 4 mL water was added to the homogenized mixture and the resulting solution was vortexed, then centrifuged at 1000+g for 30 minutes. The chloroform layer was removed and dried under nitrogen to provide. . .
DETD . . . and at the end of the study (day 7), using jugular venipuncture and immediately placed into separated Vacutainer® tubes containing EDTA anticoagulant, and processed for plasma. The plasma was aspirated and divided into two aliquots (≥0.3 ml each) and each aliquot. . .
DETD A: Preparation of stock solution:

0.1, 1, 10, 100, 1000 ng/μL in 50:50 methanol:water (1000 in DMSO) for standards.
1, 10, 100. . .
DETD B: Plasma standard curve and QC preparation: stock solution spiked in matrix identical to samples.

Concentration of standard curve:
0, 1, 2.5, 5, 10, 25, 50,. . .
DETD C: Internal Standard Solution: 0.1 ng/μL of Compound Y in acetonitrile.
DETD . . . 1) Pipette 40 μL of sample into a 1 mL 96-well plate.
2) Add 150 μL of internal standard solution to each well.
3) Gently vortex plate for 1 minute.
4) Centrifuge samples for 10 minutes (Eppendorf 5810. . .
IT 50-47-5, Desipramine 50-49-7, Imipramine 50-58-8, Phendimetrazine tartrate 58-55-9, Theophylline, biological studies 90-84-6, Diethylpropion 122-09-8, Phentermine 262-20-4, Phenoxathiin 299-45-6 302-79-4, Retinoic acid 458-24-2, Fenfluramine 465-65-6, Naloxone 537-46-2, Methamphetamine 569-59-5, Phenindamine tartrate 634-03-7, Phendimetrazine 637-07-0, Clofibrate 3239-44-9, Dexfenfluramine 6493-05-6, Pentoxifylline 11041-12-6, Cholestyramine 14721-66-5, Phytanic acid 14838-15-4, Phenylpropanolamine 16590-41-3, Naltrexone 16617-07-5 17397-89-6, Cerulenin 18464-39-6, Caroxazone 21489-20-3, Talsupram 22232-71-9, Mazindol 24526-64-5, Nomifensine 25812-30-0, Gemfibrozil 29218-27-7, Toloxatone 30299-08-2, Clinofibrate 37762-06-4, Zaprinast 41859-67-0, Bezafibrate 49562-28-9, Fenofibrate 52214-84-3, Ciprofibrate 54403-19-9 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 55096-26-9, Nalmefene 60719-84-8, Amrinone 60762-57-4, Pirlindole 61413-54-5, Rolipram 61869-08-7, Paroxetine 63638-91-5, Brofaromine 68550-75-4, Cilostamide 69047-39-8, Binifibrate 71320-77-9, Moclobemide 75330-75-5, Lovastatin 76990-56-2, Milacemide 77518-07-1, Amiflamine 78415-72-2, Milrinone 79617-96-2, Sertraline 79902-63-9, Simvastatin 81093-37-0, Pravastatin 91406-11-0, Esuprone 93957-54-1, Fluvastatin 94011-82-2, Bazinaprine 96206-92-7, 2-Methyl-6-(phenylethynyl)-pyridine 96609-16-4, Lifibrol 96829-58-2,

Orlistat 96829-59-3, Lipstatin 97240-79-4, Topiramate 103878-84-8, Lazabemide 106650-56-0, Sibutramine 117854-28-1, Befol 121062-08-6, Melanotan-II 127697-55-6, 4-[(E)-2-(5,6,7,8-Tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid 134523-00-5, Atorvastatin 134564-82-2, Befloxatone 139755-83-2, Sildenafil 145599-86-6, Cerivastatin 147511-69-1, Pitavastatin 153259-65-5, Cilomilast 163222-33-1, Ezetimibe 168273-06-1, Rimonabant 169494-85-3, Leptin 175553-48-7, Butabindide 180003-17-2, Oleoyl-estrone 287714-41-4, Rosuvastatin 329205-68-7, 3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]pyridine 444069-80-1, Axokine 879083-15-5, P 57
(codrug; preparation of 1-((1-[(2-amino-6-methyl-4-pyridinyl)methyl]-4-fluoro-4-piperidinyl)carbonyl)-4-[2-(2-pyridinyl)-3H-imidazo[4,5-b]pyridin-3-yl]piperidine as histamine H3 receptor modulator)

L9 ANSWER 6 OF 15 USPATFULL on STN

ACCESSION NUMBER: 2007:303296 USPATFULL
TITLE: (S)-N-methylnaltrexone
INVENTOR(S): Boyd, Thomas A., Grandview, NY, UNITED STATES
Wagoner, Howard, Warwick, NY, UNITED STATES
Sanghvi, Suketu P., Kendall Park, NJ, UNITED STATES
Verbicky, Christopher, Broadalbin, NY, UNITED STATES
Andruski, Stephen, Clifton Park, NY, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070265293	A1	20071115
APPLICATION INFO.:	US 2006-441452	A1	20060525 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-684570P	20050525 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WOLF GREENFIELD & SACKS, P.C., 600 ATLANTIC AVENUE, BOSTON, MA, 02210-2206, US
NUMBER OF CLAIMS: 78
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 3572
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The composition in some embodiments is a solution, in others an oil, in others a cream, and in still others a solid or semi-solid. In one important embodiment,. . .

SUMM . . . that is enteric coated, a composition that is a controlled release or sustained release formulation, a composition that is a solution, a composition that is a topical formulation, a composition that is a suppository, a composition that is lyophilized, a composition. . .

DETD . . . be used to at least partially isolate S-MNTX from NMP. Upon mixing one or more of these solvents with a solution of S-MNTX in NMP, a light colored solid may develop that becomes an oil over time.

DETD Counterions of the S-MNTX salt can be exchanged for alternative counterions. When an alternative counterion is desired, an aqueous solution of an S-MNTX salt can be passed over an anion exchange resin column to exchange some or all of the. . . on a cation exchange resin and can then be exchanged by removing the S-MNTX from the resin

with a salt solution that includes a preferred anion, such as bromide or chloride, forming the desired S-MNTX salt in solution .

DETD One aspect of the invention is a method of resolving and identifying S-MNTX and R-MNTX in a solution of MNTX. The S-MNTX also is useful in HPLC assay methods of quantifying an amount of S-MNTX in a composition. . .

DETD Aqueous formulations may include a chelating agent, a buffering agent, an anti-oxidant and, optionally, an isotonicity agent, preferably pH adjusted to between 3.0 and 3.5. Examples of such formulations that are stable to autoclaving and long term storage are. . .

DETD Chelating agents include, for example, ethylenediaminetetraacetic* ** ***acid (EDTA) and derivatives thereof, citric acid and derivatives thereof, niacinamide and derivatives thereof, sodium desoxycholate and derivatives thereof, and L-glutamic acid,. . .

DETD . . . cryoprotecting agent such as mannitol, or lactose, sucrose, polyethylene glycol, and polyvinyl pyrrolidines. Cryoprotecting agents which result in a reconstitution pH of 6.0 or less are preferred. The invention therefore provides a lyophilized preparation of therapeutic agent(s) of the invention. The. . .

DETD . . . The therapeutic agent(s) of the invention can be added to such well known formulations. It can be mixed together in solution or semi-solid solution in such formulations, can be provided in a suspension within such formulations or could be contained in particles within such. . .

DETD . . . art. Immediate release is obtainable by conventional tablets with binders which dissolve in the stomach. Coatings which dissolve at the pH of the stomach or which dissolve at elevated temperatures will achieve the same purpose. Release only in the intestine is achieved using conventional enteric coatings such as pH sensitive coatings which dissolve in the pH environment of the intestine (but not the stomach) or coatings which dissolve over time. Release throughout the gastrointestinal tract is. . .

DETD . . . the formulation. The coated pellets can be fashioned to immediately release the therapeutic agent(s) of the invention based on temperature, pH or the like. The pellets also can be configured so as to delay the release of the therapeutic agent(s) of. . .

DETD . . . erodible, nonerodible, biodegradable, or nonbiodegradable material or combinations thereof. The particles may be microcapsules which contain the antagonist in a solution or in a semi-solid state. The particles may be of virtually any shape.

DETD . . . the first is a delayed release system designed to release a drug in response to, for example, a change in pH; the second is a timed-release system designed to release a drug after a predetermined time; and the third is a. . .

DETD . . . of a delayed release system is one that uses, for example, an acrylic or cellulosic coating material and dissolves on pH change. Because of ease of preparation, many reports on such "enteric coatings" have been made. In general, an enteric coating. . .

DETD . . . A coating which remains intact for at least 2 hours, in contact with artificial gastric juices such as HCl of pH 1 at 36 to 38° C. and thereafter disintegrates within 30 minutes in

artificial intestinal juices such as a KH.sub.2PO.sub.4 buffered solution of pH 6.8 is one example. One such well known system is EUDRAGIT material, commercially available and reported on by Behringer, Manchester. . .

DETD . . . should be applied to a sufficient thickness such that the entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. It is expected that any anionic polymer exhibiting a pH -dependent solubility profile can be used as an enteric coating in the practice of the present invention. The selection of the. . .

DETD . . . carboxyl groups to ester groups is approximately 1:1. Further, the copolymer is known to be insoluble in gastrointestinal fluids having pH below 5.5, generally 1.5-5.5, i.e., the pH generally present in the fluid of the upper gastrointestinal tract, but readily soluble or partially soluble at pH above 5.5, i.e., the pH generally present in the fluid of lower gastrointestinal tract. Another particular methacrylic acid polymer is EUDRAGIT S, which differs from. . . L-30D in that the ratio of free carboxyl groups to ester groups is approximately 1:2. EUDRAGIT S is insoluble at pH below 5.5, but unlike EUDRAGIT L-30D, is poorly soluble in gastrointestinal fluids having a pH in the range of 5.5 to 7.0, such as in the small intestine. This copolymer is soluble at pH 7.0 and above, i.e., the pH generally found in the colon. EUDRAGIT S can be used alone as a coating to provide drug delivery in the large intestine. Alternatively, EUDRAGIT S, being poorly soluble in intestinal fluids below pH 7, can be used in combination with EUDRAGIT L-30D, soluble in intestinal fluids above pH 5.5, in order to provide a delayed release composition which can be formulated to deliver the active agent to various. . . in the art that both EUDRAGIT L-30D and EUDRAGIT S can be replaced with other pharmaceutically acceptable polymers having similar pH solubility characteristics. In certain embodiments of the invention, the preferred enteric coating is ACRYL-EZE.TM. (methacrylic acid co-polymer type C; Colorcon,. . .

DETD . . . A semipermeable membrane allows for the passage of water inside the coated device to dissolve the drug. The dissolved drug solution diffuses out through the semipermeable membrane. The rate of drug release depends upon the thickness of the coated film and. . .

DETD . . . emulsions, non-aqueous microemulsions and combinations thereof. The various forms of the nasal delivery systems can include a buffer to maintain pH, a pharmaceutically acceptable thickening agent and a humectant. The pH of the buffer can be selected to optimize the absorption of the therapeutic agent(s) across the nasal mucosa.

DETD . . . buffering agents can be selected such that when the formulation is delivered into the nasal cavity of a mammal, selected pH ranges are achieved therein upon contact with, e.g., a nasal mucosa. In the present invention, the pH of the compositions should be maintained from about 2.0 to about 6.0. It is desirable that the pH of the compositions is one which does not cause significant irritation to the nasal mucosa of a recipient upon administration.

DETD . . . for example, a patch, bioadhesive, dressing or bandage. It may be aqueous or non-aqueous; it may be formulated as a solution, emulsion, dispersion, a suspension or any other mixture.

DETD For local internal administration, such as intra-articular administration, the compositions are preferably formulated as a solution or a suspension in an aqueous-based medium, such as isotonically buffered saline or are combined with a biocompatible support or. . .

DETD . . . applied to the eyes and mucosa. Solutions, particularly those intended for ophthalmic use, may be formulated as 0.01%-10% isotonic solutions, pH about 5-7, with appropriate salts, and preferably containing one or more of the compounds herein at a concentration of about. . . No. 5,116,868, which describes typical compositions of ophthalmic irrigation solutions and solutions for topical application]. Such solutions, which have a pH adjusted to about 7.4, contain, for example, 90-100 mM sodium chloride, 4-6 mM dibasic potassium phosphate, 4-6 mM dibasic sodium. . .

DETD Gel compositions can be formulated by simply admixing a suitable thickening agent to the previously described solution or suspension compositions. Examples of suitable thickening agents have been previously described with respect to the lotions.

DETD . . . kit 10 also includes a vial 14 containing S-MNTX tablets which comprise pellets, some of which are enterically coated with pH sensitive material and some of which are constructed and arranged to release the S-MNTX immediately in the stomach. The kit. . .

DETD . . . preparation is optional. The diluent vial contains a diluent such as physiological saline for diluting what could be a concentrated solution or lyophilized powder of S-MNTX. The instructions can include instructions for mixing a particular amount of the diluent with a. . .

DETD . . . removing the NMP. In each case, the product and starting material were precipitated from the mixture and NMP remained in solution. Analysis of the supernatant liquid and the precipitated material by HPLC showed no significant difference between the two.

DETD . . . prepared with deionized (DI) water). The column was washed with DI water (approximately 10 L) until the eluent reached a pH of 6-7.

DETD . . . methanol to transfer the mixtures and rinse the tubes. The methanol was removed under reduced pressure and the resulting NMP solution was treated with isopropyl acetate (900 mL), which resulted in both solid and oily precipitates. The oil was agitated with. . . collected in the filter paper was combined with the original solid, using methanol to aid in the recovery. The resulting solution was concentrated to a dark, viscous oil. The oil was dissolved into 20% aqueous methanol containing 0.2% HBr (20 mL). . . (5+25 cm). The column was eluted with DI water until no MNTX was detectable in the eluted stream. The aqueous solution was concentrated and the residue was dissolved into DI water (10 mL), which was purified by chromatography further using the. . .

DETD . . . HBr (approximately 100 vol, prepared with DI water). The column was washed with DI water until the eluent reached a pH of 6-7.

DETD . . . was eluted with DI water and was rinsed until no UV active material was detected (254 nm). The resulting aqueous solution was concentrated and the residue was dissolved in IPA (5 vol) with a minimum amount of methanol to achieve solution. The solvent was stripped to remove traces of water and the resulting solid was dissolved in hot methanol (3 vol. . . approximately 50° C.).

An ambient temperature mixture of methylene chloride/isopropyl alcohol (CH.sub.2Cl.sub.2/IPA) (6 vol/1 vol) was added and the resulting solution was allowed to stand under ambient conditions until crystallization began. The mixture was then kept in a -20° C. freezer. . . .

DETD . . . suspended in 20-ml organ baths filled with an oxygenated (95% O.sub.2 and 5% CO.sub.2) and pre-warmed (37° C.) physiological salt solution of the following composition (in mM): NaCl 118.0, KCl 4.7, MgSO.sub.4 1.2, CaCl.sub.2 2.5, KH.sub.2PO.sub.4 1.2, NaHCO.sub.3 25.0 and glucose 11.0 (pH 7.4). Additional experimental conditions were as described in Hutchinson et al. (1975) Brit. J. Pharmacol., 55: 541-546.

DETD . . . at concentrations of 1.0, 3.0, or 10.0 mg/kg. A control group of rats received 2 mL/kg of a 0.9% saline solution (n=10). After 15 minutes, rats were subcutaneously injected with saline (1 mL/kg) or morphine (3 mg/kg). A 10% suspension of. . .

DETD . . . and placed in individual squares. The test or control article are administered and after the appropriate absorption time, acetic acid solution are administered intraperitoneally. Ten minutes after the i.p. injection of acetic acid, the number of writhes are recorded for a. . .

DETD . . . and placed in individual squares. The test or control article are administered and after the appropriate absorption time, the PPQ solution (0.02% aqueous solution) is administered intraperitoneally. Each animal is observed closely for ten minutes for exhibition of writhing.

CLM What is claimed is:
25. The composition of claim 13, wherein the composition is a solution.

CLM What is claimed is:
41. The pharmaceutical composition of claim 27 wherein the composition is a solution.

IT 916045-21-1P, (17S)-N-Methylnaltrexone bromide
(preparation of (17S)-N-methylnaltrexones with opioid receptor binding activity for therapeutic use in the treatment of central nervous system disorders and diarrhea)

IT 916045-19-7P, (17S)-N-Methylnaltrexone iodide
(preparation of (17S)-N-methylnaltrexones with opioid receptor binding activity for therapeutic use in the treatment of central nervous system disorders and diarrhea)

L9 ANSWER 7 OF 15 USPATFULL on STN
ACCESSION NUMBER: 2007:296970 USPATFULL
TITLE: Methods and Compositions for Treating Conditions
INVENTOR(S): Skubatch, Hanna, Seattle, WA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070259818	A1	20071108
APPLICATION INFO.:	US 2007-692847	A1	20070328 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2006-743881P	20060328 (60)

US 2006-829830P 20061017 (60)
US 2006-865337P 20061110 (60)
US 2006-868882P 20061206 (60)
US 2006-870052P 20061214 (60)
US 2006-871420P 20061221 (60)
US 2007-884376P 20070110 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WILSON SONSINI GOODRICH & ROSATI, 650 PAGE MILL ROAD, PALO ALTO, CA, 94304-1050, US
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Page(s)
LINE COUNT: 6202
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . maleimide; formation of mercurial derivatives using 4-chloromercuribenzoate, 4-chloromercuriphenylsulphonic acid, phenylmercury chloride, 2-chloromercuri-4-nitrophenol and other mercurials; carbamoylation with cyanate at alkaline pH. In any of the analogs herein, any modification of cysteine residues preferably do not affect the ability of the peptide. . .

DETD . . . powder which may contain any or all of the following: 1-50 mM histidine, 0.1%-2% sucrose, and 2-7% mannitol, at a pH range of 4.5 to 5.5 that is combined with buffer prior to use. After pharmaceutically and physiologically acceptable compositions have. . .

DETD Formulations for topical administration can use a carrier that is a solution, emulsion, and ointment or gel base. The base, for example, may comprise one or more of the following: petrolatum, lanolin,. . .

DETD . . . weight (less than about 10 residues) polypeptides, polypeptides, amino acids, carbohydrates including glucose, sucrose or dextrins, chelating agents such as EDTA, glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with nonspecific serum albumin are exemplary appropriate diluents.. . .

DETD The composition may be in the form of a liquid, e.g., an elixir, syrup, solution, emulsion or suspension. The liquid may be for oral administration or for delivery by injection, as two examples. When intended. . .

DETD In humans, the few microbes that manage to cross the barriers of skin, mucus, cilia, and pH are usually eliminated by innate immune system, which commence immediately upon pathogen entry. If phagocytosis cannot rapidly eliminate pathogen, inflammation. . .

DETD Binding is generally allowed to occur under solution conditions and for an amount of time sufficient to detect the bound ligand. An appropriate amount of time may generally. . .

DETD . . . (18° C.) cycles and 80% RH. Once a week plants were supplied with water and modified one-half strength Hoagland nutrient solution: 2 mM KNO 5 mM Ca(NO.sub.3).sub.2 and trace elements, pH 7.

DETD . . . in 0.01% Silwet L77 (v/v) (a surfactant) and distilled water 5 weeks after sowing. The bacterial suspension or a control solution (0.01% Silwet L77 in water) was then sprayed on the plant once.

IT 62-67-9, Nalorphine 465-65-6, Naloxone 578-68-7, 4-Aminoquinoline 615-16-7, 2-Benzimidazolinone 3572-80-3, Cyclazocine 4629-80-5, 1,3-Dimethyl-4-piperidinone 16590-41-3, Naltrexone 16617-07-5

36292-66-7, Ethylketocyclazocine 53179-11-6, Loperamide 55096-26-9, Nalmefene 56649-76-4, Mr 2266 58786-99-5, Butorphanol tartrate 59381-63-4 67025-97-2, β-Naltrexamine 72782-05-9, β-Funaltrexamine 73232-52-7, Methylnaltrexone 73674-85-8, Naloxazone 93302-47-7, Naloxone methiodide 103429-32-9, CTAP 105618-26-6, Nor-binaltorphimine 105618-27-7, Binaltorphimine 111555-53-4, Naltrindole 111555-58-9, Naltriben 118111-54-9, Cyprodime 129468-28-6, 7-Benzylidenenaltrexone 146369-65-5 156053-89-3, Alvimopan 156727-74-1, SNC 80 219655-56-8, 5'-Guanidinonaltrindole 244218-51-7 248273-61-2, SoRI 9409 256640-45-6, J-113397 288621-65-8 371980-98-2, SB-612111 785835-79-2, JDTic 871246-90-1D, triethylene glycol derivative 951260-91-6
(antagonist for co-treatment; opioid-related peptides and compns. for treating conditions in plants and animals)

L9 ANSWER 8 OF 15 USPATFULL on STN
ACCESSION NUMBER: 2007:141477 USPATFULL
TITLE: Prodrugs of active agents
INVENTOR(S): Jenkins, Thomas E., La Honda, CA, UNITED STATES
PATENT ASSIGNEE(S): Pharmacofore, Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070123468	A1	20070531
APPLICATION INFO.:	US 2006-508042	A1	20060821 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-711438P	20050819 (60)
	US 2005-711862P	20050825 (60)
	US 2006-760762P	20060120 (60)
	US 2006-799532P	20060510 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MORGAN, LEWIS & BOCKIUS, LLP, ONE MARKET SPEAR STREET TOWER, SAN FRANCISCO, CA, 94105, US
NUMBER OF CLAIMS: 35
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 2805
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . or enzymatically. In some embodiments, the cleavable moiety is cleaved enzymatically. Generally, the compounds described herein are stable in aqueous solution, but not so stable that the cleavable moiety can not be cleaved chemically (e.g., hydrolysis) or enzymatically. In some embodiments,. . .
DETD . . . and the like. The present pharmaceutical compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents may be used.
DETD . . . other embodiments, enteric-coated preparations can be used for oral sustained release administration. Coating materials include, for example, polymers with a pH-dependent solubility (i.e., pH-controlled release), polymers with a slow or pH -dependent rate of swelling, dissolution or erosion (i.e.,

time-controlled release), polymers that are degraded by enzymes (i.e., enzyme-controlled release) and polymers. . .

DETD . . . or diluents include water, saline, alkyleneglycols (e.g., propylene glycol), polyalkylene glycols (e.g., polyethylene glycol) oils, alcohols, slightly acidic buffers between pH 4 and pH 6 (e.g., acetate, citrate, ascorbate at between about 5 mM to about 50 mM), etc. Additionally, flavoring agents, preservatives, coloring. . .

DETD . . . alcohol, water, polyethylene glycol or a perfluorocarbon). Optionally, another material may be added to alter the aerosol properties of the solution or suspension of compositions and/or compounds disclosed herein. In some embodiments, this material is liquid such as an alcohol, glycol,. . .

DETD For injection, compounds disclosed herein may be formulated in aqueous solutions, such as physiologically compatible buffers such as Hanks' solution, Ringer's solution, physiological saline buffer or in association with a surface-active agent (or wetting agent or surfactant) or in the form of. . . with a surface-active agent may comprise between 0.05 and 5% surface-active agent or between 0.1 and 2.5% surface-active agent. The solution may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, compounds disclosed herein may be in powder form. . .

DETD . . . the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. In some embodiments, EDTA is added as a preservative.

DETD . . . compositions thereof may be administered to a subject by intravenous bolus injection, continuous intravenous infusion, oral tablet, oral capsule, oral solution, intramuscular injection, subcutaneous injection, transdermal absorption, buccal absorption, intranasal absorption, inhalation, sublingual, intracerebrally, intravaginally, rectally, topically, particularly to the ears,. . .

DETD Amine (122 mg, 1 mmol) was added to a solution of acid A (342 mg, 1 mmol) in a mixture of methylene chloride (5 ml) and dimethylformamide (1 ml) followed. . .

DETD . . . and PCl.sub.3 was added dropwise. The reaction was stirred for 1 h at 0° C. then poured into a saturated solution of NaHCO.sub.3 and extracted with ethyl acetate (3+80 ml). The combined organic layers were dried over Na2SO4, filtered, and concentrated. . .

DETD Codeine (290 mg, 0.97 mmol) was added to a solution of benzyl chloride C dissolved in acetonitrile (10 ml) at room temperature. The reaction was stirred for several days at. . . codeine quaternary salt (97% pure by HPLC analysis). 4.1 mg of this material was deprotected via exposure to an aqueous solution of K.sub.2CO.sub.3 (4.0 mg) in water (200 ul) for 18 hours to afford the desired product D. The identity of. . .

DETD Hydromorphone (29 mg, 0.1 mmol) was added to a solution of (S)-N-(α,ω,ω)-tris(Boc)-2-amino-N-methyl-N-(4-(chloromethylphenyl)-5-guanidinopentanamide (68 mg, 0.11 mmol) and lithium bromide (9.0 mg, 0.1 mmol) in 1 ml of anhydrous acetonitrile. The. . .

DETD . . . . mmol) was dissolved in 4 ml of dichloromethane and 1 ml of trifluoroacetic acid was added dropwise to the above solution. The reaction mixture was stirred for 2 hours; the solvents were removed in vacuum and the product was purified by. . .

DETD To 20 μL of the compound opioid prodrug Z (100 mM stock solution in DMSO) in 975 μL reaction buffer (12 mM CaCl.sub.2, 5 mM Tris-HCl pH 8.0) is added 5 μL Type 1 bovine trypsin (1.0 mg/mL Type 1, bovine, Sigma Chemical Company). As the reaction. . . disappearance of prodrug and/or the appearance of parent (hydrocodone). This concentration of trypsin (5 μL/mL of a 2.5 mg/mL stock solution) is set to 1+. Subsequent experiments that vary trypsin concentration are multiples of this concentration (e.g. 0.5+, 2+, 4+).

IT 51-64-9DP, Dextroamphetamine, prodrugs 57-27-2DP, Morphine, prodrugs, preparation 57-42-1DP, Meperidine, prodrugs 62-67-9DP, Nalorphine, prodrugs 64-13-1DP, p-Methoxyamphetamine, prodrugs 76-41-5DP, Oxymorphone, prodrugs 76-42-6DP, Oxycodone, prodrugs 76-99-3DP, Methadone, prodrugs 77-07-6DP, Levorphanol, prodrugs 113-45-1DP, Methylphenidate, prodrugs 115-37-7DP, Thebaine, prodrugs 125-28-0DP, Dihydrocodeine, prodrugs 125-29-1DP, Hydrocodone, prodrugs 300-62-9DP, Amphetamine, prodrugs 437-38-7DP, Fentanyl, prodrugs 465-65-6DP, Naloxone, prodrugs 466-97-7DP, Normorphine, prodrugs 467-14-1DP, Neopine, prodrugs 469-62-5DP, Propoxyphene, prodrugs 537-46-2DP, Methamphetamine, prodrugs 561-27-3DP, Diacetylmorphine, prodrugs 1083-09-6DP, 2,4,5-Trimethoxyamphetamine, prodrugs 4764-17-4DP, 3,4-Methylenedioxyamphetamine, prodrugs 14357-76-7DP, Dihydroetorphine, prodrugs 14357-78-9DP, Diprenorphine, prodrugs 14521-96-1DP, Etorphine, prodrugs 15588-95-1DP, 2,5-Dimethoxy-4-methylamphetamine, prodrugs 16590-41-3DP, Naltrexone, prodrugs 20594-83-6DP, Nalbuphine, prodrugs 27203-92-5DP, Tramadol, prodrugs 40431-64-9DP, Methyl D-phenidate, prodrugs 42408-82-2DP, Butorphanol, prodrugs 43033-72-3DP, Levomethadyl acetate hydrochloride, prodrugs 51931-66-9DP, Tilidine, prodrugs 52485-79-7DP, Buprenorphine, prodrugs 55096-26-9DP, Nalmefene, prodrugs 56030-54-7DP, Sufentanil, prodrugs 59708-52-0DP, Carfentanil, prodrugs 61380-40-3DP, Lofentanil, prodrugs 68616-83-1DP, Penomorphone, prodrugs 71195-58-9DP, Alfentanil, prodrugs 73232-52-7DP, Methyl naltrexone, prodrugs 78995-14-9DP, β-Hydroxy-3-methylfentanyl, prodrugs 83387-25-1DP, N-Methylnaltrexone, prodrugs 132875-61-7DP, Remifentanil, prodrugs 926624-80-8P 926624-84-2P
(prodrugs of pharmacol. active agents)

L9 ANSWER 9 OF 15 USPATFULL on STN

ACCESSION NUMBER:	2007:114872 USPATFULL
TITLE:	Synthesis of R-N-methylnaltrexone
INVENTOR(S):	Doshan, Harold D., Riverside, CT, UNITED STATES Perez, Julio, Tarrytown, NY, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070099946	A1	20070503
APPLICATION INFO.:	US 2006-441395	A1	20060525 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-684616P	20050525 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	WOLF GREENFIELD & SACKS, PC, FEDERAL RESERVE PLAZA, 600 ATLANTIC AVENUE, BOSTON, MA, 02210-2206, US

NUMBER OF CLAIMS: 53
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Page(s)
LINE COUNT: 2524
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . foregoing compositions that comprise MNTX in R configuration with respect to nitrogen in some important embodiments is a crystal, a solution, or a bromide salt of MNTX. In other embodiments, the foregoing compositions are pharmaceutical preparations, preferably in effective amounts and. . .

SUMM . . . composition is a packaged unit dosage or a multi-unit dosage. In yet another embodiment the packaged unit dosage is a solution . The pharmaceutical composition in one embodiment is a solution . In another embodiment it is an enteric coated solid dosage form. In still another embodiment it is a sustained release. . .

DETD One aspect of the invention is a method of resolving and identifying R-MNTX and S-MNTX in a solution of MNTX. The R-MNTX also is useful in HPLC assay methods of quantifying an amount of R-MNTX in a composition. . .

DETD Aqueous formulations may include a chelating agent, a buffering agent, an anti-oxidant and, optionally, an isotonicity agent, preferably pH adjusted to between 3.0 and 3.5. Examples of such formulations that are stable to autoclaving and long term storage are. .

DETD Chelating agents include, for example, ethylenediaminetetraacetic* ** ***acid (EDTA) and derivatives thereof, citric acid and derivatives thereof, niacinamide and derivatives thereof, sodium desoxycholate and derivatives thereof, and L-glutamic acid,. . .

DETD . . . cryoprotecting agent such as mannitol, or lactose, sucrose, polyethylene glycol, and polyvinyl pyrrolidines. Cryoprotecting agents which result in a reconstitution pH of 6.0 or less are preferred. The invention therefore provides a lyophilized preparation of therapeutic agent(s) of the invention. The. . .

DETD . . . The therapeutic agent(s) of the invention can be added to such well known formulations. It can be mixed together in solution or semi-solid solution in such formulations, can be provided in a suspension within such formulations or could be contained in particles within such. . .

DETD . . . art. Immediate release is obtainable by conventional tablets with binders which dissolve in the stomach. Coatings which dissolve at the pH of the stomach or which dissolve at elevated temperatures will achieve the same purpose. Release only in the intestine is achieved using conventional enteric coatings such as pH sensitive coatings which dissolve in the pH environment of the intestine (but not the stomach) or coatings which dissolve over time. Release throughout the gastrointestinal tract is. . .

DETD . . . the formulation. The coated pellets can be fashioned to immediately release the therapeutic agent(s) of the invention based on temperature, pH or the like. The pellets also can be configured so as to delay the release of the therapeutic agent(s) of. . .

DETD . . . erodible, nonerodible, biodegradable, or nonbiodegradable material or combinations thereof. The particles may be microcapsules which contain the antagonist in a solution or in a semi-solid

state. The particles may be of virtually any shape.

DETD . . . the first is a delayed release system designed to release a drug in response to, for example, a change in pH; the second is a timed-release system designed to release a drug after a predetermined time; and the third is a. . .

DETD . . . of a delayed release system is one that uses, for example, an acrylic or cellulosic coating material and dissolves on pH change. Because of ease of preparation, many reports on such "enteric coatings" have been made. In general, an enteric coating. . . .

DETD . . . A coating which remains intact for at least 2 hours, in contact with artificial gastric juices such as HCl of pH 1 at 36 to 38° C. and thereafter disintegrates within 30 minutes in artificial intestinal juices such as a KH.sub.2PO.sub.4 buffered solution of pH 6.8 is one example. One such well known system is EUDRAGIT material, commercially available and reported on by Behringer, Manchester. . .

DETD . . . should be applied to a sufficient thickness such that the entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. It is expected that any anionic polymer exhibiting a pH -dependent solubility profile can be used as an enteric coating in the practice of the present invention. The selection of the. . .

DETD . . . carboxyl groups to ester groups is approximately 1:1. Further, the copolymer is known to be insoluble in gastrointestinal fluids having pH below 5.5, generally 1.5-5.5, i.e., the pH generally present in the fluid of the upper gastrointestinal tract, but readily soluble or partially soluble at pH above 5.5, i.e., the pH generally present in the fluid of lower gastrointestinal tract. Another particular methacrylic acid polymer is EUDRAGIT S, which differs from. . . L-30D in that the ratio of free carboxyl groups to ester groups is approximately 1:2. EUDRAGIT S is insoluble at pH below 5.5, but unlike EUDRAGIT L-30D, is poorly soluble in gastrointestinal fluids having a pH in the range of 5.5 to 7.0, such as in the small intestine. This copolymer is soluble at pH 7.0 and above, i.e., the pH generally found in the colon. EUDRAGIT S can be used alone as a coating to provide drug delivery in the large intestine. Alternatively, EUDRAGIT S, being poorly soluble in intestinal fluids below pH 7, can be used in combination with EUDRAGIT L-30D, soluble in intestinal fluids above pH 5.5, in order to provide a delayed release composition which can be formulated to deliver the active agent to various. . . in the art that both EUDRAGIT L-30D and EUDRAGIT S can be replaced with other pharmaceutically acceptable polymers having similar pH solubility characteristics. In certain embodiments of the invention, the preferred enteric coating is ACRYL-EZE.TM. (methacrylic acid co-polymer type C; Colorcon,. . .

DETD . . . A semipermeable membrane allows for the passage of water inside the coated device to dissolve the drug. The dissolved drug solution diffuses out through the semipermeable membrane. The rate of drug release depends upon the thickness of the coated film and. . .

DETD . . . emulsions, non-aqueous microemulsions and combinations thereof. The various forms of the nasal delivery systems can include a buffer to maintain pH, a pharmaceutically acceptable thickening agent and a humectant. The pH of the buffer can be selected to optimize the absorption of the therapeutic agent(s) across

the nasal mucosa.

DETD . . . buffering agents can be selected such that when the formulation is delivered into the nasal cavity of a mammal, selected pH ranges are achieved therein upon contact with, e.g., a nasal mucosa. In the present invention, the pH of the compositions should be maintained from about 2.0 to about 6.0. It is desirable that the pH of the compositions is one which does not cause significant irritation to the nasal mucosa of a recipient upon administration.

DETD . . . for example, a patch, bioadhesive, dressing or bandage. It may be aqueous or non-aqueous; it may be formulated as a solution, emulsion, dispersion, a suspension or any other mixture.

DETD For local internal administration, such as intra-articular administration, the compositions are preferably formulated as a solution or a suspension in an aqueous-based medium, such as isotonically buffered saline or are combined with a biocompatible support or. . .

DETD . . . applied to the eyes and mucosa. Solutions, particularly those intended for ophthalmic use, may be formulated as 0.01%-10% isotonic solutions, pH about 5-7, with appropriate salts, and preferably containing one or more of the compounds herein at a concentration of about. . . No. 5,116,868, which describes typical compositions of ophthalmic irrigation solutions and solutions for topical application]. Such solutions, which have a pH adjusted to about 7.4, contain, for example, 90-100 mM sodium chloride, 4-6 mM dibasic potassium phosphate, 4-6 mM dibasic sodium. . .

DETD Gel compositions can be formulated by simply admixing a suitable thickening agent to the previously described solution or suspension compositions. Examples of suitable thickening agents have been previously described with respect to the lotions.

DETD . . . kit 10 also includes a vial 14 containing R-MNTX tablets which contain pellets, some of which are enterically coated with pH sensitive material and some of which are constructed and arranged to release the R-MNTX immediately in the stomach. The kit. . .

DETD . . . pharmaceutical preparation is optional. The diluents vial contains diluents such as physiological saline for diluting what could be a concentrated solution or lyophilized powder of R-MNTX. The instructions can include instructions for mixing a particular amount of the diluents with a. . .

DETD 3-O-Isobutyryl-Naltrexone (2). To a solution of compound (1) (1.62 g, 4.75 mmol) in anhydrous tetrahydrofuran (THF) (120 mL) at 0° C. was added triethylamine (NEt3). . .

DETD . . . resin slurry. The resin bed was washed with 1.0N aqueous hydrobromic acid (200 ml) and then sterile water until the pH of the aqueous eluate was pH 6-7. Approximately 1.5 L of water was required.

DETD . . . 10 ml and then cooled under nitrogen in ice/water. Some white precipitate was formed but clearly much solid remained in solution. The mixture was then concentrated by evaporation to give a slightly colored gum. This was triturated with methanol (3 ml+2).. . .

DETD . . . was dissolved in methanol (50 ml) and filtered through a glass sinter. The filtrate was concentrated to approximately 1 ml solution and a further portion of methanol (1 ml) was added to triturate the solid. The supernatant liquors were decanted as. . .

DETD 6. Adjust the pH of the solution to pH

3.25.
DETD Disodium edetate=0.75 mg/ml Added in step 2
DETD When all excipients and drug have been added, step 6, pH of the solution is adjusted by addition of acid. If a buffering agent is used in the solution, pH adjustment may not be required.
DETD A preferred manufacturing process for 100 ml of 20 mg/ml solution of R-MNTX solution is as follows:
DETD 2. Add 75 mg of disodium edetate, a chelating agent, to the tank and stir till dissolved.
DETD 6. Adjust the pH of the solution if necessary.
DETD A formula for a low citrate/EDTA formulation is listed below:

Ingredient	mg/mL	
R-MNTX	30	mg
Sodium chloride	4	mg
Citric acid	0.0875	mg
Trisodium citrate	0.0496	mg
Disodium edetate	0.75	mg
Water for injection	q.s. to 1	g

The pH of this solution is 3.5 and can withstand an autoclaving process.
DETD . . . sterile filtered Nitrogen and then seat the closures (2" Hg), then bleed to atmospheric pressure with N.sub.2 to unload. The pH of the solution after lyophilization and reconstitution is 5.0.
IT 916045-21-1P, (17S)-N-Methylnaltrexone bromide
(asym. synthesis of (17R)-N-methylnaltrexones for use in pharmaceutical compns. for treatment of gastrointestinal disorders)
IT 916055-92-0P, (17R)-N-Methylnaltrexone bromide
(asym. synthesis of (17R)-N-methylnaltrexones for use in pharmaceutical compns. for treatment of gastrointestinal disorders)
IT 916055-91-9P, (17R)-N-Methylnaltrexone iodide
(asym. synthesis of (17R)-N-methylnaltrexones for use in pharmaceutical compns. for treatment of gastrointestinal disorders)

L9 ANSWER 10 OF 15 USPATFULL on STN

ACCESSION NUMBER:	2006:131740 USPATFULL			
TITLE:	Compositions and methods for treating or preventing pain			
INVENTOR(S):	Shafer, Steven L., Mountain View, CA, UNITED STATES Flood, Pamela, Closter, NJ, UNITED STATES Jenkins, Thomas E., La Honda, CA, UNITED STATES			
PATENT ASSIGNEE(S):	Pharmacofore, Inc. (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20060111382	A1	20060525	
APPLICATION INFO.:	US 2005-131778	A1	20050517	(11)
	NUMBER	DATE		

PRIORITY INFORMATION: US 2004-572129P 20040517 (60)
US 2004-574050P 20040524 (60)
US 2004-574261P 20040524 (60)
US 2004-574167P 20040524 (60)
US 2004-574135P 20040524 (60)
US 2004-574106P 20040524 (60)
US 2004-574049P 20040524 (60)
US 2004-574257P 20040524 (60)
US 2004-574262P 20040524 (60)
US 2004-574369P 20040524 (60)
US 2004-574023P 20040524 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Sunil K. Singh, Dorsey & Whitney LLP, Intellectual Property Department, Four Embarcadero Center, Suite 3400, San Francisco, CA, 94111-4187, US
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 1472
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . and the like. The present pharmaceutical compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents may be used.

DETD . . . other embodiments, enteric-coated preparations can be used for oral sustained release administration. Coating materials include, for example, polymers with a pH-dependent solubility (i.e., pH-controlled release), polymers with a slow or pH -dependent rate of swelling, dissolution or erosion (i.e., time-controlled release), polymers that are degraded by enzymes (i.e., enzyme-controlled release) and polymers. . .

DETD . . . or diluents include water, saline, alkyleneglycols (e.g., propylene glycol), polyalkylene glycols (e.g., polyethylene glycol) oils, alcohols, slightly acidic buffers between pH 4 and pH 6 (e.g., acetate, citrate, ascorbate at between about 5 mM to about 50 mM), etc. Additionally, flavoring agents, preservatives, coloring. . .

DETD . . . alcohol, water, polyethylene glycol or a perfluorocarbon). Optionally, another material may be added to alter the aerosol properties of the solution or suspension of compositions and/or compounds disclosed herein. In some embodiments, this material is liquid such as an alcohol, glycol,. . .

DETD . . . injection, compositions and/or compounds disclosed herein may be formulated in aqueous solutions, such as physiologically compatible buffers such as Hanks' solution, Ringer's solution, physiological saline buffer or in association with a surface-active agent (or wetting agent or surfactant) or in the form of. . . with a surface-active agent may comprise between 0.05 and 5% surface-active agent or between 0.1 and 2.5% surface-active agent. The solution may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively compositions and compounds may be in powder form. . .

DETD . . . the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. In some embodiments, EDTA is added as a preservative.

DETD . . . compositions thereof may be administered to a subject by intravenous bolus injection, continuous intravenous infusion, oral tablet, oral capsule, oral solution, intramuscular injection, subcutaneous injection, transdermal absorption, buccal absorption, intranasal absorption, inhalation, sublingual, intracerebrally, intravaginallly, rectally, topically, particularly to the ears,. . .

DETD The components of the kit may be provided in one or more liquid solutions, preferably, an aqueous solution, more preferably, a sterile aqueous solution. The components of the kit may also be provided as solids, which may be converted into liquids by addition of. . .

IT 51-84-3, Acetylcholine, biological studies 54-11-5, Nicotine 54-77-3, Dmpp 57-42-1, Meperidine 62-49-7, Choline 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone 77-07-6, Levorphanol 115-37-7, Thebaine 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 359-83-1, Pentazocine 437-38-7, Fentanyl 465-65-6, Naloxone 466-97-7, Normorphine 466-99-9, Hydromorphone 467-14-1, Neopine 469-62-5, Propoxyphene 485-35-8, Cytisine 538-79-4, Meta-nicotine 561-27-3, Diacetylmorphine 14357-76-7, Dihydroetorphine 14357-78-9, Diprenorphine 14521-96-1, Etorphine 16590-41-3, Naltrexone 20594-83-6, Nalbuphine 27203-92-5, Tramadol 42408-82-2, Butorphanol 43033-72-3, Levomethadyl acetate hydrochloride 51931-66-9, Tilidine 52485-79-7, Buprenorphine 55096-26-9, Nalmefene 56030-54-7, Sufentanil 59708-52-0, Carfentanil 61380-40-3, Lofentanil 68616-83-1, Pentamorphone 71195-58-9, Alfentanil 73232-52-7, Methyl naltrexone 78995-14-9, β-Hydroxy-3-methylfentanyl 83387-25-1, N-Methylnaltrexone 132875-61-7, Remifentanil 140111-52-0, Epibatidine 147402-53-7, Abt-418 148372-04-7 156223-05-1, Gts-21 156743-99-6, Dmac
(compns. and methods for treating or preventing pain)

L9 ANSWER 11 OF 15 USPATFULL on STN

ACCESSION NUMBER:	2005:130630 USPATFULL
TITLE:	Multi-arm polymer prodrugs
INVENTOR(S):	Zhao, Xuan, Huntsville, AL, UNITED STATES Bentley, Michael D., Huntsville, AL, UNITED STATES Ren, Zhongxu, Madison, AL, UNITED STATES Viegas, Tacey X., Madison, AL, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20050112088	A1	20050526
APPLICATION INFO.:	US 2004-943799	A1	20040917 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-503673P	20030917 (60)
	US 2004-584308P	20040630 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	NEKTAR THERAPEUTICS, 150 INDUSTRIAL ROAD, SAN CARLOS, CA, 94070, US
NUMBER OF CLAIMS:	56
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	7 Drawing Page(s)
LINE COUNT:	2484

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . or segment will transmit at least about 75%, more preferably at least about 95% of light, transmitted by the same solution after filtering. On a weight basis, a water-soluble polymer or segment thereof will preferably be at least about 35% (by. . .

DETD . . . phospholipids such as lecithin and other phosphatidylcholines, phosphatidylethanolamines, fatty acids and fatty esters, steroids (e.g., cholesterol)), and chelating agents (e.g., EDTA, zinc and other such suitable cations). Other pharmaceutical excipients and/or additives suitable for use in the compositions according to the. . .

DETD . . . In general, the compositions are prepared by bringing the active compound into association with a liquid carrier to form a solution or a suspension, or alternatively, bring the active compound into association with formulation components suitable for forming a solid, optionally. . .

DETD A syrup may be made by adding the active compound to a concentrated aqueous solution of a sugar, for example sucrose, to which may also be added any accessory ingredient(s). Such accessory ingredients may include. . .

DETD . . . purified aqueous solutions of the active agent with preservative agents and isotonic agents. Such formulations are preferably adjusted to a pH and isotonic state compatible with the nasal mucous membranes.

DETD Ophthalmic formulations are prepared by a similar method to the nasal spray, except that the pH and isotonic factors are preferably adjusted to match that of the eye.

DETD Pharmaceutical formulations are also provided which are suitable for administration as an aerosol, by inhalation. These formulations comprise a solution or suspension of the desired polymer conjugate or a salt thereof. The desired formulation may be placed in a small. . .

DETD . . . t-Boc-Glycine (0.3408 mmoles), and 0.021 g DMAP (0.1704 mmoles) were dissolved in 13 mL of anhydrous dichloromethane (DCM). To the solution was added 0.070 g DCC (0.3408 mmoles) dissolved in 2 mL of anhydrous DCM. The solution was stirred overnight at room temperature. The solid was removed through a coarse frit, and the solution was washed with 10 mL of 0.1N HCL in a separatory funnel. The organic phase was further washed with 10. . .

DETD 0.1 g t-Boc-Glycine-Irinotecan (0.137 mmoles) was dissolved in 7 mL of anhydrous DCM. To the solution was added 0.53 mL trifluoroacetic acid (6.85 mmoles). The solution was stirred at room temperature for 1 hour. The solvent was removed using rotary evaporation. The crude product was dissolved. . .

DETD . . . 0.488 mmoles), and 0.0658 g 2-hydroxybenzyltriazole (HOBT, 0.488 mmoles) were dissolved in 60 mL anhydrous methylene chloride. To the resulting solution was added 0.282 g 1,3-dicyclohexylcarbodiimide (DCC, 1.3664 mmoles). The reaction mixture was stirred overnight at room temperature. The mixture was. . .

DETD . . . g, 0.1 mol) and NaHCO.sub.3 (12.6 g, 0.15 mol) were added to 100 mL CH.sub.2Cl.sub.2 and 100 mL H.sub.2O. The solution was stirred at RT for 10 minutes, then di-tert-butyl dicarbonate (21.8 g, 0.1 mol) was added. The resulting solution was stirred at RT overnight, then extracted with CH.sub.2Cl.sub.2 (3+100 mL). The organic phases were combined and dried over anhydrous. . .

DETD . . . (14.6 g, 120 mmol) were dissolved in 200 ml anhydrous CH.sub.2Cl.sub.2. Triphosgene (5.91 g, 20 mmol) was added to the solution while stirring at room temperature. After 20 minutes,

the solution was added to a solution of irinotecan (6.0 g, 10.2 mmol) and DMAP (12.2 g, 100 mmol) in anhydrous CH.sub.2Cl.sub.2 (200 mL). The reaction was stirred at RT for 2 hrs, then washed with HCI solution (pH=3, 2L) to remove DMAP. The organic phases were combined and dried over anhydrous sodium sulfate. The dried solution was evaporated under vacuum and subjected to silica gel column chromatography (CH.sub.2Cl.sub.2:CH.sub.3OH=40:1.about.10:1) to afford 2-(2-t-Boc-aminoethoxy)ethoxycarbonyl-irinotecan (2) (4.9 g, 6.0 mmol,. . .

DETD . . . 5.75 mmol) was dissolved in 60 mL CH.sub.2Cl.sub.2, and trifluoroacetic acid (TFA) (20 mL) was added at RT. The reaction solution was stirred for 2 hours. The solvents were removed under vacuum and the residue was added to ethyl ether and. . .

DETD . . . (2.85 g, 3.44 mmol) was dissolved in 12 mL DMF and treated with 0.6 mL TEA, then added to a solution of 4-arm-PEG.sub.20k-SCM. The reaction was stirred at RT for 12 hrs then precipitated in Et.sub.2O to yield a solid product, which was dissolved in 500 mL IPA at 50° C. The solution was cooled to RT and the resulting precipitate collected by filtration to give 4-arm-PEG.sub.20k-glycine-irinotecan (4) (16.2 g, drug content 7.5%. . .

DETD . . . (2.85 g, 3.44 mmol) was dissolved in 12 mL DMF and treated with 0.6 mL TEA, then added to the solution of 4-arm-PEG.sub.40k-SCM. The reaction was stirred at RT for 12 hrs and then precipitated in Et.sub.2O to get solid product, which was dissolved in 1000 mL isopropyl alcohol (IPA) at 50° C. The solution was cooled to RT and the precipitate collected by filtration to gave 4-arm-PEG.sub.40k-glycine-irinotecan (4) (g, drug content 3.7% based on. . .

IT 76-41-5DP, Oxymorphone, polymer derivs. 76-42-6DP, Oxycodone, polymer derivs. 76-57-3DP, Codeine, polymer derivs. 79-39-0DP, Methacrylamide, hydroxyalkyl derivs., polymers, drug conjugates 79-41-4DP, Methacrylic acid, hydroxyalkyl esters, polymers, drug conjugates 124-94-7DP, Triamcinolone, polymer derivs. 465-65-6DP, Naloxone, polymer derivs. 4291-63-8DP, Cladribine, polymer derivs. 9002-89-5DP, Polyvinyl alcohol, drug derivs. 9003-01-4DP, Polyacrylic acid, drug derivs. 9003-39-8DP, Polyvinylpyrrolidone, drug derivs. 15663-27-1DP, cis-Platin, polymer derivs. 28902-82-1DP, Poly(N-acryloylmorpholine), drug derivs. 41575-94-4DP, Carboplatin, polymer derivs. 51333-22-3DP, Budesonide, polymer derivs. 61825-94-3DP, Oxaliplatin, polymer derivs. 73232-52-7DP, Methylnaltrexone, polymer derivs. 75607-67-9DP, Fludarabine phosphate, polymer derivs. 85721-33-1DP, Ciprofloxacin, polymer derivs. 90566-53-3DP, Fluticasone, polymer derivs. 95058-81-4DP, Gemcitabine, polymer derivs. 135729-61-2DP, Palonosetron, polymer derivs. 151096-09-2DP, Moxifloxacin, polymer derivs. 848779-38-4P
(water-soluble multi-arm polymer prodrugs)

L9 ANSWER 12 OF 15 USPATFULL on STN
ACCESSION NUMBER: 2005:5049 USPATFULL
TITLE: Use of methylnaltrexone to treat irritable bowel syndrome
INVENTOR(S): Boyd, Thomas A., Grandview, NY, UNITED STATES
Israel, Robert J., Suffern, NY, UNITED STATES
Sanghvi, Suketu P., Kendall Park, NJ, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20050004155	A1	20050106
APPLICATION INFO.:	US 2004-821813	A1	20040408 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-461608P	20030408 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Edward R. Gates, Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA, 02210
NUMBER OF CLAIMS: 111
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 1973
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . embodiments, the pharmaceutical preparation is administered intrarectally, intranasally and transdermally. In some embodiments, the pharmaceutical preparation is formulated as a solution. In other embodiments the pharmaceutical preparation is formulated as a suppository. In other embodiments the pharmaceutical preparation is formulated as. . .

SUMM . . . Formulations for oral administration include a capsule (e.g., a solid-filled capsule), a powder, a granule, a crystal, a tablet, a solution, an extract, a suspension, a soup, a syrup, an elixir, a tea, a liquid-filled capsule, an oil, a chewable tablet,. . .

DETD [0080] Osmotic laxatives include, but are not limited to, lactulose, sorbitol (d-glucitol), polyethylene glycol solution, and glycerin (glycerol).

DETD . . . agent, and a preservative. In the case of quaternary amine derivatives of noroxymorphone, a chelating agent can be added and pH can be adjusted to between 3.0 and 3.5. Preferred such formulations that are stable to autoclaving and long term storage. . .

DETD [0100] Chelating agents include: ethylenediaminetetraacetic acid (EDTA) and derivatives thereof, citric acid and derivatives thereof, niacinamide and derivatives thereof, sodium desoxycholate and derivatives thereof.

DETD . . . art. Immediate release is obtainable by conventional tablets with binders which dissolve in the stomach. Coatings which dissolve at the pH of the stomach or which dissolve at elevated temperatures will achieve the same purpose. Release only in the intestine is achieved using conventional enteric coatings such as pH sensitive coatings which dissolve in the pH environment of the intestine (but not the stomach) or coatings which dissolve over time. Release throughout the gastrointestinal tract is. . .

DETD . . . material of the suppository. The coated pellets can be fashioned to immediately release the peripheral opioid antagonist based on temperature, pH or the like. The pellets also can be configured so as to delay the release of the peripheral opioid antagonist,. . .

DETD . . . erodible, nonerodible, biodegradable, or nonbiodegradable material or combinations thereof. The particles may be microcapsules which contain the antagonist in a solution or in a semi-solid

state. The particles may be of virtually any shape.

DETD . . . types: the first is a delayed release system designed to release a drug in response to, for example, change in pH or temperature; the second is a timed-release system designed to release a drug after a predetermined time; and the third. . .

DETD . . . of a delayed release system is one that uses, for example, an acrylic or cellulosic coating material and dissolves on pH change. Because of ease of preparation, many reports on such "enteric coatings" have been made. In general, an enteric coating. . .

DETD . . . A coating which remains intact for at least 2 hours, in contact with artificial gastric juices such as HCl of pH 1 at 36 to 38° C. and thereafter disintegrates within 30 minutes in artificial intestinal juices such as a KH.sub.2PO.sub.4 buffered solution of pH 6.8 is one example. One such well known system is EUDRAGIT material, commercially available and reported on by Behringer, Manchester. . .

DETD . . . should be applied to a sufficient thickness such that the entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. It is expected that any anionic polymer exhibiting a pH -dependent solubility profile can be used as an enteric coating in the practice of the present invention The selection of the. . .

DETD . . . carboxyl groups to ester groups is approximately 1:1. Further, the copolymer is known to be insoluble in gastrointestinal fluids having pH below 5.5, generally 1.5-5.5, i.e., the pH generally present in the fluid of the upper gastrointestinal tract, but readily soluble or partially soluble at pH above 5.5, i.e., the pH generally present in the fluid of lower gastrointestinal tract. Another particular methacrylic acid polymer is EUDRAGIT S, which differs from. . . L-30D in that the ratio of free carboxyl groups to ester groups is approximately 1:2. EUDRAGIT S is insoluble at pH below 5.5, but unlike EUDRAGIT L-30D, is poorly soluble in gastrointestinal fluids having a pH in the range of 5.5 to 7.0, such as in the small intestine. This copolymer is soluble at pH 7.0 and above, i.e., the pH generally found in the colon. EUDRAGIT S can be used alone as a coating to provide drug delivery in the large intestine. Alternatively, EUDRAGIT S, being poorly soluble in intestinal fluids below pH 7, can be used in combination with EUDRAGIT L-30D, soluble in intestinal fluids above pH 5.5, in order to provide a delayed release composition which can be formulated to deliver the active agent to various. . . in the art that both EUDRAGIT L-30D and EUDRAGIT S can be replaced with other pharmaceutically acceptable polymers having similar pH solubility characteristics.

DETD . . . described above. Semipermeable membranes allow passage of water inside the coated device and then dissolve the drug. The dissolved drug solution then diffuses out through the semipermeable membrane. The rate of drug release therefore depends upon the thickness of the coated. . .

DETD . . . emulsions, non-aqueous microemulsions and combinations thereof. The various forms of the nasal delivery systems can include a buffer to maintain pH, a pharmaceutically acceptable thickening agent and a humectant. The pH of the buffer can be selected to optimize the absorption of the therapeutic agent(s) across the nasal mucosa.

DETD . . . buffering agents can be selected such that when the formulation

is delivered into the nasal cavity of a mammal, selected pH ranges are achieved therein upon contact with, e.g., a nasal mucosa. In the present invention, the pH of the compositions should be maintained from about 2.0 to about 6.0. It is desirable that the pH of the compositions is one which does not cause significant irritation to the nasal mucosa of a recipient upon administration.

DETD . . . preparation is optional. The vial 14 contains a diluent such as physiological saline for diluting what could be a concentrated solution or lyophilized preparation of methylnaltrexone contained in vial 12. The instructions can include instructions for mixing a particular amount of. . .

DETD . . . injection. Methylnaltrexone was dissolved in isotonic saline for administration in this study. No other excipients were present in the administered solution. Oral-cecal transit time was measured prior to the first dose and after the last dose, following repeated dosing for 3. . .

DETD [0148]

	mg per tablet
Ingredients used (Trade name)	
Methylnaltrexone	225
Microcrystalline cellulose (Avicel PH 101)	80
Polyvinylpyrrolidone (Povidone K30)	10.50
Croscarmellose sodium (Ac-Di-Sol SD-711)	8
Dibasic Calcium Phosphate (Emcompress) NO AVICEL PH 200 WAS USED	25
Magnesium Stearate (Hyqual)	1.7
Opadry II Clear	7.00
Water	as needed
Equipment used	
Key KG-5 Granulator	to make granules . . .. . .

DETD [0152] 2. Granulate the above mixture using a solution of Povidone in water.

DETD [0160] 10. Coat the tablets with a solution of Opadry II Clear in water using a O'Hara Labcoat.

DETD [0169] 3. Granulate the above mixture using a solution of polyvinylpyrrolidone in water (10 g in 100 ml).

CLM What is claimed is:
11. The method of claim 1 wherein the pharmaceutical preparation is administered as a solution.

CLM What is claimed is:
104. The pharmaceutical preparation of claim 102 wherein the formulation is selected from the group consisting of a capsule, a powder, a granule, a crystal, a tablet, a solution, an extract, a suspension, a soup, a syrup, an elixir, a tea, a liquid-filled capsule, an oil, a chewable tablet,. . .

CLM What is claimed is:
. . . 106. The pharmaceutical preparation of claim 105 wherein the formulation is selected from the group consisting of a suspension, a solution, a suppository, an oil, and an enema.

IT 577-11-7, Docusate sodium 25322-68-3, PEG 3350 33522-95-1D,

Noroxymorphone, quaternary derivs. 73232-52-7, Methylnaltrexone 145158-71-0
(methylnaltrexone or other peripheral opioid antagonist to treat irritable bowel syndrome)

L9 ANSWER 13 OF 15 USPATFULL on STN
ACCESSION NUMBER: 2004:335712 USPATFULL
TITLE: Pharmaceutical formulation
INVENTOR(S): Sanghvi, Suketu P., Kendall Park, NJ, UNITED STATES
Boyd, Thomas A., Grandview, NY, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20040266806	A1	20041230
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PRIORITY INFORMATION:	US 2003-461611P	20030408 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Edward R. Gates, Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA, 02210
NUMBER OF CLAIMS: 210
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 1639
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . existed. Methylnaltrexone apparently was assumed to have a structure that was inherently stable. The stability of a pharmaceutical composition in solution, however, is not necessarily predictable either over time when stored at room temperature or when autoclaved.

SUMM . . . acts both centrally and peripherally. It differs structurally from methylnaltrexone and would be expected to have a different stability in solution. An allegedly stable formulation of naloxone is described in U.S. Pat. No. 5,866,154.

SUMM [0006] In one aspect, the invention provides a composition or preparation that is a solution of methylnaltrexone or a salt thereof, wherein the preparation after autoclaving has a concentration of methylnaltrexone degradation products that does. . . agent, a buffering agent, an anti-oxidant, a cryoprotecting agent, an isotonicity agent and an opioid. The preferred chelating agent is disodium edetate or a derivative thereof. The disodium edetate preferably is at a concentration ranging from between 0.001 and 100 mg/ml, more preferably 0.05 to 25.0 mg/ml, and even. . .

SUMM [0007] The composition or preparation preferably has a pH that does not exceed 4.25. More preferably, the pH ranges from 2.0 to 4.0, 3.0 to 4.0, and most preferably, from 3.0 to 3.5.

SUMM [0008] According to another aspect of the invention, a composition or preparation is provided, which includes a solution of methylnaltrexone or a salt thereof, wherein the preparation after storage at about room temperature for six months has a. . . as described above. The preferred buffering agent and concentrations are as described above. Preferably, the composition or preparation has a pH that does not exceed 4.25. The preferred pHs and ranges are

as described above.

SUMM . . . According to another aspect of the invention, a stable composition or preparation is provided. The composition or preparation is a solution of methylnaltrexone or a salt thereof wherein the pH is below 4.25. Preferably, the pH is between 2.75 and 4.25, more preferably, between 3.0 and 4.0, and most preferably, between 3.0 and 3.5. According to conventional procedures, pH can be adjusted with an acid. Examples of acids useful for this purpose include hydrochloric acid, citric acid, sulfuric acid,. . .

SUMM . . . According to another aspect of the invention, a stable composition or preparation is provided. The composition or preparation is a solution of methylnaltrexone or salt thereof, wherein the solution further comprises a chelating agent in an amount sufficient to inhibit degradation of the methylnaltrexone or salt thereof, whereby the. . .

SUMM [0011] According to another aspect of the invention, a composition or preparation is provided. The composition or preparation is a solution of methylnaltrexone or salt thereof in at least one methylnaltrexone degradation inhibiting agent. The agent can be any one of, any combination of, or all of a chelating agent, a buffering agent, and an antioxidant, provided that the solution has a pH ranging from 2.0 to 6.0. The degradation inhibiting agent is present in an amount sufficient to render the composition or. . . autoclaving. The composition or preparation further may include either or both of an isotonicity agent and an opioid. Preferably, the pH of the solution is between 2.75 and 4.25, more preferably, between 3.0 and 4.0, and most preferably, between 3.0 and 3.5.

SUMM [0016] In any one of the foregoing embodiments, the solution of methylnaltrexone or salt thereof may be contained in a sealed container such as a bottle, an infusion bag, a. . . a septum, an ampoule, an ampoule with a septum, or a syringe. The container may include indicia indicating that the solution has been autoclaved or otherwise subjected to a sterilization technique.

SUMM . . . stable lyophilized formulation of methylnaltrexone, wherein the formulation upon reconstitution and water at a concentration of 20 mg/ml has a pH of between 2 and 6. In some embodiments, the formulation upon reconstitution has a pH of about 2, about 3, about 4, about 5, or about 6. The formulation can include a cryoprotecting agent present. . .

SUMM . . . an antioxidant, and combinations thereof, wherein the degradation inhibiting agent is present in an amount sufficient to render stable the solution of the product containing a concentration of 20 mg/ml methylnaltrexone in water. Preferably, the product when in solution at a concentration of 20 mg/ml methylnaltrexone yields a pH of between 2 and 6.

SUMM . . . of the invention, a pharmaceutical preparation is provided. The pharmaceutical preparation contains methylnaltrexone, sodium chloride, citric acid, trisodium citrate, and disodium edetate . In one important embodiment, the methylnaltrexone is present between 20 and 40 mg/ml, the sodium chloride is present between 2. . . acid is present between 0.05 and 0.1 mg/ml, the trisodium citrate is present between 0.025 and 0.075 mg/ml, and the disodium edetate is present between 0.5 and 1.0 mg/ml.

SUMM [0022] The chelating agent may be any pharmaceutically acceptable

chelating agent. Common chelating agents include ethylenediaminetetraacetic acid (EDTA) and derivatives thereof, citric acid and derivatives thereof, niacinamide and derivatives thereof, and sodium desoxycholate and derivatives thereof. The preferred chelating agent is disodium edetate.

SUMM [0028] According to another aspect of the invention, a method is provided for preparing an autoclaved preparation of a solution of methylnaltrexone or salts thereof, whereby the autoclaved preparation has a concentration of methylnaltrexone degradation products that does not exceed 2% of the methylnaltrexone or salt thereof in the preparation. The method involves providing a solution, having a pH of 4.25 or less, of methylnaltrexone or a salt thereof, and being substantially free of methylnaltrexone degradation products, and autoclaving the solution. The solution can contain, optionally, any one of, any combination of, or all of a chelating agent, an isotonicity agent, a buffering agent, an antioxidant, a cryoprotecting agent, and an opioid. Preferably, the pH of the solution ranges from 2.0 to 4.0. More preferably, from 3.0 to 4.0, and most preferably from 3.0 to 3.5. Preferred chelating. . .

SUMM . . . products that does not exceed 2% of the methylnaltrexone or salt thereof in the preparation. The method involves providing a solution containing methylnaltrexone or salt thereof and a chelating agent, the solution being substantially free of methylnaltrexone degradation products, and then autoclaving the solution. The chelating agent is present in an amount sufficient to protect the preparation against substantial unwanted degradation of methylnaltrexone or its salt, and maintain the solution to be substantially free of methylnaltrexone degradation products. Preferred chelating agents and concentrations thereof are as described above. The preparation. . . Preferred buffering agents, isotonicity agents, antioxidants and opioids, as well as concentrations, are as described above. Preferred pHs of the solution likewise are as described above. Preferably, the degradation products after autoclaving do not exceed 1.5%, 1%, 0.5%, 0.25% or even. . .

SUMM . . . the invention, a method is provided for inhibiting the formation of methylnaltrexone degradation products in a preparation that is a solution of methylnaltrexone or salts thereof. The method involves preparing an aqueous solution containing at least one methylnaltrexone degradation inhibiting agent selected from the group consisting of a chelating agent, a buffering agent,. . . an antioxidant, a cryoprotecting agent, and combinations thereof. A powdered source of methylnaltrexone or salt thereof is dissolved into the solution to form the preparation. The preparation has or is adjusted without addition of a pH-adjusting base to have a pH of between 2 and 6. More preferably, the pharmaceutical preparation is adjusted to have a pH ranging from 3 to 5, more preferably, 3 to 4, and most preferably, 3.0 to 3.5. An isotonicity agent may be added to the solution. Likewise, an opioid may be added to the solution.

SUMM . . . to another aspect of the invention, a method is provided for preparing a stable pharmaceutical preparation that is an aqueous solution of methylnaltrexone or salts thereof to inhibit formation of methylnaltrexone degradation products. A solution is provided containing methylnaltrexone or salts thereof and at least

one methylnaltrexone degradation inhibiting agent. The solution is processed under at least one sterilization technique prior to and/or after terminal filling the solution in a sealable container to form the stable pharmaceutical preparation, wherein the method is carried out without the addition of pH-adjusting base to the solution. The methylnaltrexone degradation inhibiting agent can be selected from the group consisting of a chelating agent, a buffering agent, an. . . buffering agents, antioxidants, isotonicity agents, cryoprotecting agents, and opioids are as described above. Preferred concentrations are as described above. The solution may be processed to adjust the pH. This is preferably done using an acid. Most preferably, the solution is adjusted to a range between a pH of 2 and 6, more preferably, between 3 and 5, 3 and 4, and most preferably between 3.0 and 3.5.. . .

SUMM . . . are provided. In one embodiment, the formulation made by dissolving methylnaltrexone diluted in water, to which mannitol is added. The solution is then filter sterilized followed by lyophilization. Therefore, the product may be provided in lyophilized form, and in combination with. . .

SUMM . . . mixing the preparation and the diluent. The diluent can be any pharmaceutically acceptable diluent. Well known diluents include 5% dextrose solution and physiological saline solution. The container can be an infusion bag, a sealed bottle, a vial, a vial with a septum, an ampoule, an. . .

DETD [0042] Applicants have discovered that during the autoclaving process, methylnaltrexone in aqueous solution tends to degrade to a surprising extent. The amount of degradation resulting from simple autoclaving (122° C., 15 lbs. pressure. . . observed. The degradant identified by the 0.72 RRT peak appears in small amounts, 0.074, immediately upon dissolving the methylnaltrexone into solution and increases overtime with storage or autoclaving 0.25%. The degradant identified by the 0.89 RRT peak appears only after storage. . . of time such as 6 months, 12 months or even two years. Degradation occurs without regard to whether the aqueous solution was previously autoclaved or filter sterilized. It would be desirable to stabilize formulations of methylnaltrexone such that following the autoclaving. . .

DETD . . . methylnaltrexone degradation products resulting from such conditions are not more than 2% of the total methylnaltrexone present in a given solution. By stable solution of methylnaltrexone, it also is meant that following storage of an unautoclaved solution at room temperature for twelve months, the methylnaltrexone degradation products resulting from such conditions are not more than 2% of the total methylnaltrexone present in a given solution. By stable solutions of methylnaltrexone, it is also meant that following storage of an unautoclaved solution at room temperature for two months, the methylnaltrexone degradation products resulting from such conditions are not more than 1.0% of the total methylnaltrexone present in a given solution. By stable lyophilized formulations of methylnaltrexone, it is meant that following lyophilization and storage at room temperature of methylnaltrexone for. . . methylnaltrexone degradation products resulting from such conditions are not more than 1.0% of the total methylnaltrexone present in a given solution.

DETD [0044] It was surprisingly discovered that pH alone can solve the problem of excessive methylnaltrexone degradation products. In

particular, it was discovered that when the pH of a methylnaltrexone solution containing 2 mg/mL of methylnaltrexone was at about 4.25 pH or less, there was a steep drop-off in the amount of methylnaltrexone degradation products following autoclaving. When the pH of the solution containing methylnaltrexone was adjusted to between 3.5 and 4.0, then the total percentage of degradants fell below 2%, and in certain instances even below 1.39%. When the pH was adjusted to between 3.0 and 3.5, the percentage of total degradants dropped to about 0.23% after autoclaving. It was also noted that there was a significant drop, before a plateau, when the pH of the methylnaltrexone solution was brought to below 6.0 prior to autoclaving. Adjusting pHs to between 4.25 and 6 was not sufficient to produce stable formulations of methylnaltrexone (through the adjustment of pH alone). As will be seen below, however, manipulating other parameters in concert with pH resulted in stable formulations of methylnaltrexone anywhere in a range from a pH of 2.0 to 6.0. The benefits of a low pH on the stability of methylnaltrexone formulations persisted in the presence of chelating agents, isotonicity agents, buffering agents, and antioxidants. Thus, the invention in one aspect provides stable formulations of methylnaltrexone in solution, wherein the pH is below 4.25, preferably between 3.0 and 4.0, and most preferably between 3.0 and 3.5.

DETD [0045] Applicants also noted that despite setting the pH of a methylnaltrexone solution at points between 3.0 and 6.0 using a pH-adjusting acid or pH-adjusting base prior to autoclaving and despite the benefits obtained from lower pH, the pH of the autoclaved sample drifted almost immediately to about 7.0. It was therefore tested, in particular, whether buffering agents could eliminate the pH drift that resulted from autoclaving without negatively affecting the ability to protect against heat degradation resulting from autoclaving. Applicants discovered that buffering agents indeed could be employed to stabilize the pH of methylnaltrexone solutions throughout the autoclaving process without permitting degradation products to exceed acceptable minimums. Buffers were used in concentrations. . . buffer did not seem to alter in any material respects the amount of degradation products resulting from autoclaving the methylnaltrexone solution, resulting in less than 0.23% of degradation products at pH of 3.5. The addition of acetate buffer, however, appeared to increase somewhat the amount of methylnaltrexone degradation products, although not to unacceptable levels, resulting in less than 1.39% of degradation products at pH of 3.6. Nonetheless, citrate buffer surprisingly is preferable to acetate buffer. The preferred citrate buffer range is between about 2. . .

DETD . . . surprisingly, that a chelating agent alone was capable of reducing the amount of degradation products to acceptable levels. In particular, pH was not adjusted and disodium edetate was added at concentrations of 0.01, 0.1, 0.25, 0.5, 0.75, and 1.0 mg/mL. The disodium edetate stabilized methylnaltrexone against heat degradation in a concentration-dependent manner. As little as 0.01 mg/mL had a substantial effect on the. . . point at approximately 0.3-0.4 mg/mL where the total degradants became slightly under 0.5% and leveled off with increasing amounts of disodium edetate. Thus, disodium edetate alone was sufficient to render stable an unbuffered

solution of methylnaltrexone with no adjustment to pH. This was a surprising result.

DETD [0048] Applicants believe that the result is not limited to disodium edetate. Instead, other chelating agents well known to those of ordinary skill in the art will be useful according to the. . . chemicals which form water soluble coordination compounds with metal ions in order to trap or remove the metal irons from solution, thereby avoiding the degradative effects of the metal ions. Chelating agents include ethylenediaminetetraacetic acid (also synonymous with EDTA, edetic acid, versene acid, and sequestrene), and EDTA derivatives, such as dipotassium edetate, disodium edetate, edetate calcium disodium, sodium edetate, trisodium edetate, and potassium edetate. Other chelating agents include citric acid and derivatives thereof. Citric acid also is known as citric acid monohydrate. Derivatives of. . . trisodiumcitrate-dihydrate. Still other chelating agents include niacinamide and derivatives thereof and sodium desoxycholate and derivatives thereof. A synergistic effect of pH and disodium edetate was also observed. At pH 3-3.5, in the presence of citrate buffer (25 mM), and 0.01 mg/mL disodium edetate, the total degradants after autoclaving amounted to less than 0.4%. Under the same conditions, except increasing the concentration of disodium edetate to 1 mg/mL, there was no detectable difference. That is, the degradants were on the order of approximately 0.4% after autoclaving. The circumstance, however, differed when pH was adjusted upwardly to between 6.0 and 7.0 in an unbuffered system. In particular, at a pH adjusted upwardly to between 6.0 and 7.0, the total degradants were above 3-6% at a concentration of 0.01 mg/mL disodium edetate and approximately 2.8% at 1.0 mg/mL disodium edetate. This at first glance appears anomalous with the results described above, where disodium edetate alone was sufficient to bring total degradants under 0.5% at concentrations above approximately 0.3 disodium edetate mg/mL. It was discovered, however, that the increase in degradation was due to the addition of a pH -adjusting base to the solution containing methylnaltrexone to upwardly adjust the pH to 6.0-7.0. Therefore, it was discovered unexpectedly that the addition of a pH-adjusting base, such as sodium hydroxide, to a solution containing methylnaltrexone should be avoided in order to minimize the presence of degradants.

DETD [0049] The same results were achieved through a combination of acetate buffer and disodium edetate at 0.01 mg/mL and 1.0 mg/mL, although, once again, citrate buffer seemed to work surprisingly better than acetate buffer in protecting methylnaltrexone from heat degradation. Higher levels of disodium edetate in the presence of acetate buffer could compensate, however, for the differential effect that was observed when using citrate buffer. . .

DETD . . . antioxidants will be useful according to the invention. Antioxidants are substances capable of inhibiting oxidation by removing free radicals from solution. Antioxidants are well known to those of ordinary skill in the art and include materials such as ascorbic acid, ascorbic. . .

DETD . . . a compound which is added to the pharmaceutical preparation to

increase the osmotic pressure to that of 0.9% sodium chloride solution, which is iso-osmotic with human extracellular fluids, such as plasma. Preferred isotonicity agents are sodium chloride, mannitol, sorbitol, lactose, dextrose. . .

DETD [0053] In view of the success achieved with disodium edetate alone in an unbuffered system, it would have been expected that stable formulations could be prepared at virtually any pH simply by optimizing the various potential methylnaltrexone degradation inhibiting agents. Such agents include those as described above, that is, chelating agents, buffering agents, antioxidants, and the like. It was discovered, however, that stable formulations of methylnaltrexone in solution could not be obtained with such degradation inhibiting agents at pHs above 6. Thus, in one aspect of the invention, stable pharmaceutical preparations containing methylnaltrexone in solution are permitted, wherein the solution further includes an agent selected from the group consisting of a chelating agent, a buffering agent, an antioxidant, and combinations thereof, provided that the solution has a pH ranging from between 2 to 6.

DETD . . . that is, such solutions contain less than 2% methylnaltrexone degradation products compared to the total amount of methylnaltrexone in the solution.

DETD . . . the harmful effects of freezing. Such agents also can prevent caking and flaking, which can be problematic in reconstituting a solution and in manufacturing processing. Important cryoprotecting agents are mannitol, lactose, sucrose, polyethylene qlycol and polyvinyl pyrrolidine. Most preferred is mannitol. It is believed that cryoprotecting agents which result in a reconstitution pH of 6.0 and higher or which are basic will contribute also to degradation of methylnaltrexone due to pH effects discussed above. Thus, preferred cryoprotecting agents are those which, together with the other components of the formulation, result in a pH in the preferred ranges described above. Preferably, the cryoprotecting agent is neutral or acidic.

DETD [0056] The amount of methylnaltrexone in the solution is effective to treat completely, ameliorate, or even prevent conditions associated with activation of endogenous opioid receptors, in particular, peripheral. . .

DETD . . . preparation is optional. The vial 14 contains a diluent such as physiological saline for diluting what could be a concentrated solution of methylnaltrexone contained in vial 12. The instructions can include instructions for mixing a particular amount of the diluent with. . .

DETD . . . do not exceed 2% of the methylnaltrexone or salt thereof in the preparation. Aqueous solutions of methylnaltrexone are prepared. A pH-adjusting acid is added to adjust the pH to 4.25 or less, preferably to a range of between 3.0 and 3.5. The solution is then autoclaved according to standard procedures. One such procedure involves autoclaving at 122° C. and 15 pounds of pressure. . . cryoprotective agent, and an opioid. According to another aspect of the invention, a pharmaceutical preparation containing methylnaltrexone in a aqueous solution is prepared by combining a chelating agent with the methylnaltrexone solution and then autoclaving the solution. The aqueous solution of methylnaltrexone may contain any one of, any combination of or all of a buffering agent, an antioxidant, an isotonicity. . .

DETD [0068] The invention also involves methods of inhibiting the formation of methylnaltrexone degradation products in a solution containing methylnaltrexone by combining any one of, any combination of or all of a chelating agent, a buffering agent and an antioxidant with methylnaltrexone or salt thereof in solution. In one preferred embodiment, the aqueous solution containing the chelating agent, buffering agent and/or antioxidant is first prepared, then a powdered source of methylnaltrexone or salt thereof is dissolved into the aqueous solution.

DETD . . . is first prepared, then a powdered source of methylnaltrexone or salt thereof is dissolved into the gel. As used herein, solution embraces gels.

DETD . . . erodible, nonerodible, biodegradable, or nonbiodegradable material or combinations thereof. The particles may be microcapsules which contain the antagonist in a solution or in a semi-solid state. The particles may be of virtually any shape.

DETD . . . preparing stable pharmaceutical preparations containing aqueous solutions of methylnaltrexone or salts thereof to inhibit formation of methylnaltrexone degradation products. A solution is provided that contains methylnaltrexone or salts thereof and at least one methylnaltrexone inhibiting agent. The solution is processed under at least one sterilization technique prior to and/or after terminal filing the solution in the sealable container to form a stable pharmaceutical preparation, wherein the method is carried out without the addition of a pH-adjusting base to the solution.

DETD [0079] 6. Adjust the pH of the solution to pH 3.25.

DETD [0085] Exact amount of excipients to be used:

Disodium edetate = 0.75 mg/ml Added in step 2
Sodium Citrate = 0.199 mg/ml Added in step 3
Citric acid = 0.35. . .

DETD [0087] When all excipients and drug have been added, step 6, pH of the solution is adjusted by addition of acid. If a buffering agent is used in the solution, pH adjustment may not be required.

DETD [0090] 100 ml of 20 mg/ml solution of methylnaltrexone solutions

DETD [0092] 2. Add 75 mg of disodium edetate, a chelating agent, to the tank and stir till dissolved.

DETD [0096] 6. Adjust the pH of the solution if necessary.

DETD [0102] Methylnaltrexone (bromide salt) and its degradation products in an isotonic saline solution were tested upon manufacture of the solution (no added stabilizers, sterile filtered, not autoclaved) and upon storage at room temperature for 12 months using a Hewlett-Packard HP1100. . .

DETD . . . added to a suitable container, to which 150 mL of methanol and 1.0 mL of trifluoroacetic acid were added. The solution was mixed well and allowed to equilibrate to room temperature. The solution was degassed by helium sparge. Mobile phase B (methanol): Methanol was added to a suitable container and degassed by helium. . .

DETD [0119] HPLC analysis was also conducted, prior to storage, on a methylnaltrexone solution manufactured using an isotonic saline solution (no added stabilizers), sterile filtered, and autoclaved. This saline, autoclaved solution contained the degradation products formed during manufacturing or storage, as described above (data not shown).

DETD [0120] The degradation products seen with very low citrate level were the same as those seen with normal saline solution. These low citrate formulas were autoclaved and after three months the amount of degradation products seen were less than 0. 1% for each degradation product. The formula used for the citrate/EDTA formulation is listed below:

	mg/mL	
Methynaltrexone	30	mg
Sodium Chloride	4	mg
Citric acid	0.0875	mg
Trisodium Citrate	0.0496	mg
Disodium edetate	0.75	mg
Water for injection	q.s. to 1	gram

DETD [0121] The pH of this solution is 3.5 and can withstand autoclaving process.

DETD . . . following data reports the stability of lyophilized formulations of methylnaltrexone using different cryoprotecting agents.

Cryoprotecting Agent	pH	total degradation products
Mannitol	5.0	0.34%
Polyvinyl pyrrolidone	4.1	0.37%
Polyethylene glycol	5.7	0.44%
Histidine	7.4	0.55%

DETD . . .

	1	2	3	4	5	6
Key Ingredient	Monothio-glycerol	Citrate Buffer pH 3.5	Citrate Buffer pH 5	Acetate Buffer pH	Lyophilized using	Lyophilized using
	3.6 Mannitol	Lactose				
Unautoclaved	0.13	0.12	0.16	0.20	0.14	0.12
Autoclaved	0.91	0.23	0.61	1.39	n/a	n/a
Stability (2 mths	1.10	0.16	0.48. .	.		

CLM What is claimed is:

1. A pharmaceutical preparation comprising a solution of methylnaltrexone or a salt thereof, wherein the preparation after autoclaving has a concentration of methylnaltrexone degradation products that does. . .

CLM What is claimed is:

8. The pharmaceutical preparation of claim 7, wherein the chelating agent is ethylenediaminetetraacetic acid (EDTA) or a derivative thereof.

CLM What is claimed is:
10. The pharmaceutical preparation of claim 8, wherein the EDTA or derivative thereof is present in a concentration ranging from 0.001 to 100.0 mg/ml.

CLM What is claimed is:
22. The pharmaceutical preparation of claim 1, wherein the pH of the preparation does not exceed 4.25.

CLM What is claimed is:
38. The pharmaceutical preparation of claim 1, wherein the solution is provided in a vial or ampoule with a septum.

CLM What is claimed is:
39. The pharmaceutical preparation of claim 1, wherein the solution is provided in a syringe, infusion bag or sealable bottle.

CLM What is claimed is:
44. The pharmaceutical preparation of claim 1, wherein the solution is provided in a container including indicia indicating that the pharmaceutical preparation has been autoclaved.

CLM What is claimed is:
. . . methylnaltrexone degradation products that does not exceed 2% of the methylnaltrexone or salt thereof in the preparation comprising: providing a solution having a pH of 4.25 or less comprising methylnaltrexone or salt thereof and being substantially free of methylnaltrexone degradation products; and autoclaving the solution.

CLM What is claimed is:
54. The method of claim 50, wherein the solution contains a chelating agent.

CLM What is claimed is:
55. The method of claim 50, wherein the solution further comprises an isotonicity agent.

CLM What is claimed is:
56. The method of claim 50, wherein the solution comprises a buffering agent.

CLM What is claimed is:
58. The method of claim 50, wherein the solution comprises an anti-oxidant.

CLM What is claimed is:
61. The method of claim 54, wherein the chelating agent is EDTA or derivative thereof.

CLM What is claimed is:

63. The method of claim 50, further comprising lyophilizing the solution.

CLM What is claimed is:
64. The method of claim 63, further comprising adding a cryoprotecting agent to the solution.

CLM What is claimed is:
66. A method for preparing an autoclaved pharmaceutical preparation that has a concentration of methylnaltrexone degradation products that does not exceed 2% of the methylnaltrexone or salt thereof in the preparation comprising: providing a solution comprising methylnaltrexone or salt thereof and a chelating agent, the solution being substantially free of methylnaltrexone degradation products; and autoclaving the solution.

CLM What is claimed is:
67. The method of claim 66, wherein the chelating agent is EDTA or derivative thereof.

CLM What is claimed is:
68. The method of claim 67, wherein the EDTA or derivative thereof is present in a concentration ranging from 0.001 to 100.0 mg/ml.

CLM What is claimed is:
71. The method of claim 66, wherein the solution contains a buffering agent.

CLM What is claimed is:
73. The method of claim 66, wherein the solution is adjusted to have a pH of 4.25 or less.

CLM What is claimed is:
77. The method of claim 66, wherein the solution contains an anti-oxidant.

CLM What is claimed is:
78. The method of claim 66, wherein the solution contains an isotonicity agent.

CLM What is claimed is:
83. The method of claim 66, further comprising lyophilizing the solution.

CLM What is claimed is:
84. The method of claim 83, further comprising adding a cryoprotecting agent to the solution.

CLM What is claimed is:
86. A pharmaceutical preparation comprising a solution of methylnaltrexone or a salt thereof, wherein the preparation after storage at about room temperature for six months has a. . .

CLM What is claimed is:
93. The pharmaceutical preparation of claim 92, wherein the chelating agent is EDTA or derivative thereof.

CLM What is claimed is:
94. The pharmaceutical preparation of claim 93, wherein the EDTA or derivative thereof is present in a concentration ranging from 0.001 to 100.0 mg/ml.

CLM What is claimed is:
106. The pharmaceutical preparation of claim 86, wherein the pH does not exceed 4.25.

CLM What is claimed is:
129. The pharmaceutical preparation of claim 86, wherein the solution is provided in a vial or ampoule with a septum, in a syringe, an infusion bag, or a sealable bottle.
. . .
CLM What is claimed is:
133. The pharmaceutical preparation of claim 86, wherein the solution is provided in a container including indicia indicating that the solution has been autoclaved.

CLM What is claimed is:
136. A stable pharmaceutical preparation comprising a solution of methylnaltrexone or salt thereof, wherein the pH is below 4.25.

CLM What is claimed is:
140. The pharmaceutical preparation of claim 136, wherein the pH is adjusted with an acid selected from the group consisting of HCI, citric acid, sulfuric acid, acetic acid, or phosphoric. . .
CLM What is claimed is:
149. The pharmaceutical preparation of claim 147, wherein the chelating agent is selected from the group consisting of EDTA and derivatives thereof, citric acid and derivatives thereof, niacinamide and derivatives sodium desoxycholate and derivatives thereof.

CLM What is claimed is:
188. A stable pharmaceutical preparation comprising a solution of methylnaltrexone or salt thereof, wherein the solution further comprises a chelating agent in an amount sufficient to inhibit degradation of the methylnaltrexone or salt thereof, whereby the. . .
CLM What is claimed is:
189. The pharmaceutical preparation of claim 188, wherein the chelating agent is selected from the group consisting of EDTA and derivatives thereof, citric acid and derivatives thereof, niacinamide and derivatives thereof, and sodium desoxycholate and derivatives thereof.

CLM What is claimed is:
231. A pharmaceutical preparation comprising a solution of methylnaltrexone or salt thereof and at least one methylnaltrexone degradation inhibiting agent selected from the group consisting of a chelating agent, a buffering agent, an antioxidant, and combinations thereof, wherein the solution has a pH ranging from 2 to 6, wherein the degradation inhibiting agent is present in an amount sufficient to render the preparation. . .
CLM What is claimed is:
246. The pharmaceutical preparation of claim 231, wherein the

solution is provided in a container including indicia indicating the preparation has been processed under at least one sterilization technique.

CLM What is claimed is:
. . . formation of methylnaltrexone degradation products in a pharmaceutical preparation comprising methylnaltrexone or salts thereof, the method comprising: preparing an aqueous solution comprising at least one methylnaltrexone degradation inhibiting agent selected from the group consisting of a chelating agent, a buffering agent, an antioxidant, and combinations thereof, dissolving a powdered source of methylnaltrexone or salt thereof with the solution to form the pharmaceutical preparation.

CLM What is claimed is:
252. The method of claim 247, further comprising adjusting with an acid the pH of the solution or the preparation to a pH ranging from 2 to 6.

CLM What is claimed is:
255. The method of claim 247, further comprising adding an isotonicity agent to the solution.

CLM What is claimed is:
256. A method of preparing a stable pharmaceutical preparation comprising an aqueous solution of methylnaltrexone or salts thereof to inhibit formation of methylnaltrexone degradation products, comprising: providing a solution comprising methylnaltrexone or salts thereof and at least one methylnaltrexone degradation inhibiting agent; processing the solution under at least one sterilization technique prior to and/or after terminal filling the solution in a sealable container to form the stable pharmaceutical preparation, wherein the method is carried out without the addition of a pH-adjusting-base to the solution.

CLM What is claimed is:
267. The method of claim 256, wherein the initial solution is adjusted to a pH ranging from 2 to 6 prior to the processing under the at least one sterilization technique.

CLM What is claimed is:
275. The method of claim 256, wherein the initial solution further comprises an isotonicity agent.

CLM What is claimed is:
277. The method of claim 256, wherein the initial solution further comprising a cryoprotective agent.

CLM What is claimed is:
279. The method of claim 256, further comprising adding at least one opioid to the initial solution.

CLM What is claimed is:
281. The method of claim 279, wherein the opioid is solubilized in a nonaqueous solvent prior to addition to the initial solution.

CLM What is claimed is:
. . . stable lyophilized formulation of methylnaltrexone, wherein the formulation upon reconstitution in water at a concentration of 20 mg/ml has a pH of between 2 and 6.

CLM What is claimed is:
293. A product comprising a lyophilized formulation of methylnaltrexone prepared from a solution comprising the solution of claim 1.

CLM What is claimed is:
294. A product comprising a lyophilized formulation of methylnaltrexone prepared from a solution comprising the solution of claim 36.

CLM What is claimed is:
296. A product comprising a lyophilized formulation of methylnaltrexone prepared from a solution comprising the solution of claims claim 86.

CLM What is claimed is:
299. A product comprising a lyophilized formulation of methylnaltrexone prepared from a solution comprising the solution of claim 136.

CLM What is claimed is:
. . . an anti-oxidant, and combinations thereof, wherein the degradation inhibiting agent is present in an amount sufficient to render stable a solution of the product containing a concentration of 20 mg/ml methylnaltrexone.

CLM What is claimed is:
303. The product of claim 302, wherein the product when in solution at a concentration of 20 mg/ml methylnaltrexone yields a solution with a pH of between 2 and 6.

CLM What is claimed is:
. . . of claim 303, wherein the product has less than 1% methylnaltrexone degradation products when stored at room temperature in the solution for 6 months.

CLM What is claimed is:
307. A pharmaceutical preparation comprising methylnaltrexone; sodium chloride, citric acid, trisodium citrate, and disodium edetate.

CLM What is claimed is:
308. The pharmaceutical preparation of claim 307, wherein the preparation is a solution and the methylnaltrexone is present at between 20 and 40 mg/ml, the sodium chloride is present between 2 and 6. . . . acid is present between 0.05 and 0.1 mg/ml, the trisodium citrate is present between 0.025 and 0.075 mg/ml and the disodium edetate is present between 0.5 and 1.0 mg/ml.

CLM What is claimed is:
312. The kit of claim 310, wherein the diluant is selected from the

group consisting of a 5% dextrose solution and a physiological saline solution.

IT 50-21-5, Lactic acid, biological studies 50-70-4, Sorbitol, biological studies 50-81-7, Ascorbic acid, biological studies 50-99-7, Dextrose, biological studies 56-40-6, Glycine, biological studies 56-81-5, Glycerol, biological studies 57-27-2, Morphine, biological studies 57-42-1, Meperidine 60-00-4, EDTA, biological studies 62-67-9, Nalorphine 63-42-3, LActose 64-19-7, Acetic acid, biological studies 65-85-0, Benzoic acid, biological studies 68-04-2, Sodium citrate 69-65-8, Mannitol 71-00-1, Histidine, biological studies 72-17-3, Sodium lactate 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone 77-07-6, Levorphanol 77-92-9, Citric acid, biological studies 87-69-4, Tartaric acid, biological studies 98-92-0, Niacinamide 110-15-6, Succinate, biological studies 110-16-7, Maleic acid, biological studies 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 127-09-3, Sodium acetate 128-37-0, Butylated hydroxytoluene, biological studies 134-03-2, Sodium ascorbate 139-33-3, Disodium EDTA 144-14-9, Anileridine 144-55-8, NaHCO3, biological studies 149-44-0, Sodium formaldehyde sulfoxylate 149-91-7D, Gallic acid, alkyl esters 152-02-3, Levallorphan 288-32-4, Imidazole, biological studies 302-95-4, Sodium deoxycholate 359-83-1, Pentazocine 367-51-1, Sodium thioglycollate 437-38-7, Fentanyl 463-79-6, Carbonic acid, biological studies 466-99-9, Hydromorphone 469-62-5, Propoxyphene 532-32-1, Sodium benzoate 561-27-3, Heroin 915-30-0, Diphenoxylate 1477-40-3, Levomethadyl acetate 7631-90-5, Sodium bisulfite 7632-05-5, Sodium phosphate 7647-14-5, Sodium chloride, biological studies 7664-38-2, Phosphoric acid, biological studies 7681-57-4, Sodium metabisulfite 7757-83-7, Sodium sulfite 7775-14-6, Sodium dithionite 14047-56-4, Sodium succinate 15686-91-6, Propiram 20290-10-2, Morphine 6-glucuronide 20594-83-6, Nalbuphine 25013-16-5, Butylated hydroxyanisole 27203-92-5, Tramadol 38098-46-3, Monothioglycerol 39133-31-8, Trimebutine 42408-82-2, Butorphanol 51931-66-9, Tilidine 52485-79-7, Buprenorphine 53179-11-6, Loperamide 53648-55-8, Dezocine 56030-54-7, Sufentanyl 71195-58-9, Alfentanil 72782-05-9 73232-52-7, Methylnaltrexone 75684-07-0, Bremazocine 83387-25-1 123618-00-8, Fedotozine 153205-46-0, Asimadoline
(pharmaceutical formulations containing methylnaltrexone)

L9 ANSWER 14 OF 15 USPATFULL on STN
ACCESSION NUMBER: 2004:328074 USPATFULL
TITLE: Combination therapy for constipation
INVENTOR(S): Sanghvi, Suketu P., Kendall Park, NJ, UNITED STATES
Boyd, Thomas A., Grandview, NY, UNITED STATES
Maddon, Paul J., Scarsdale, NY, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20040259899	A1	20041223
APPLICATION INFO.:	US 2004-821809	A1	20040408 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-461585P	20030408 (60)
DOCUMENT TYPE:	Utility	

FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Edward R. Gates, Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA, 02210
NUMBER OF CLAIMS: 114
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 1554
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD [0054] Aqueous formulations may include a chelating agent, a buffering agent, an anti-oxidant and, optionally, an isotonicity agent, preferably pH adjusted to between 3.0 and 3.5. Preferred such formulations that are stable to autoclaving and long term storage are described. . .

DETD [0055] Chelating agents include: ethylenediaminetetraacetic acid (EDTA) and derivatives thereof, citric acid and derivatives thereof, niacinamide and derivatives thereof, sodium desoxycholate and derivatives thereof.

DETD . . . art. Immediate release is obtainable by conventional tablets with binders which dissolve in the stomach. Coatings which dissolve at the pH of the stomach or which dissolve at elevated temperatures will achieve the same purpose. Release only in the intestine is achieved using conventional enteric coatings such as pH sensitive coatings which dissolve in the pH environment of the intestine (but not the stomach) or coatings which dissolve over time. Release throughout the gastrointestinal tract is. . .

DETD . . . the material of the suppository. The coated pellets can be fashioned to immediately release the opioid antagonist based on temperature, pH or the like. The pellets also can be configured so as to delay the release of the opioid antagonist, allowing. . .

DETD . . . peripheral opioid antagonist can be added to such well known formulations. The peripheral opioid antagonist can be mixed together in solution or semi-solid solution in such formulations, can be provided in a suspension within such formulations or could be contained in particles within such. . .

DETD . . . erodible, nonerodible, biodegradable, or nonbiodegradable material or combinations thereof. The particles may be microcapsules which contain the antagonist in a solution or in a semi-solid state. The particles may be of virtually any shape.

DETD . . . first is a delayed release system designed to release a drug in response to with, for example, a change in pH; the second is a timed-release system designed to release a drug after a predetermined time; and the third is a. . .

DETD . . . of a delayed release system is one that uses, for example, an acrylic or cellulosic coating material and dissolves on pH change. Because of ease of preparation, many reports on such "enteric coatings" have been made. In general, an enteric coating. . .

DETD . . . A coating which remains intact for at least 2 hours, in contact with artificial gastric juices such as HCl of pH 1 at 36 to 38° C. and thereafter disintegrates within 30 minutes in artificial intestinal juices such as a KH.sub.2PO.sub.4 buffered solution of pH 6.8 is one example. One such well known system is EUDRAGIT material, commercially available and reported on by Boehringer, Manchester. . .

DETD . . . should be applied to a sufficient thickness such that the

entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. It is expected that any anionic polymer exhibiting a pH -dependent solubility profile can be used as an enteric coating in the practice of the present invention The selection of the. . .

DETD . . . carboxyl groups to ester groups is approximately 1:1. Further, the copolymer is known to be insoluble in gastrointestinal fluids having pH below 5.5, generally 1.5-5.5, i.e., the pH generally present in the fluid of the upper gastrointestinal tract, but readily soluble or partially soluble at pH above 5.5, i.e., the pH generally present in the fluid of lower gastrointestinal tract. Another particular methacrylic acid polymer is EUDRAGIT S, which differs from. . . L-30D in that the ratio of free carboxyl groups to ester groups is approximately 1:2. EUDRAGIT S is insoluble at pH below 5.5, but unlike EUDRAGIT L-30D, is poorly soluble in gastrointestinal fluids having a pH in the range of 5.5 to 7.0, such as in the small intestine. This copolymer is soluble at pH 7.0 and above, i.e., the pH generally found in the colon. EUDRAGIT S can be used alone as a coating to provide drug delivery in the large intestine. Alternatively, EUDRAGIT S, being poorly soluble in intestinal fluids below pH 7, can be used in combination with EUDRAGIT L-30D, soluble in intestinal fluids above pH 5.5, in order to provide a delayed release composition which can be formulated to deliver the active agent to various. . . in the art that both EUDRAGIT L-30D and EUDRAGIT S can be replaced with other pharmaceutically acceptable polymers having similar pH solubility characteristics.

DETD . . . above. Semipermeable membrane allow for the passage of water inside the coated device to dissolve the drug. The dissolved drug solution diffuses out through the semipermeable membrane. The rate of drug release depends upon the thickness of the coated film and. . .

DETD . . . emulsions, non-aqueous microemulsions and combinations thereof. The various forms of the nasal delivery systems can include a buffer to maintain pH, a pharmaceutically acceptable thickening agent and a humectant. The pH of the buffer can be selected to optimize the absorption of the therapeutic agent(s) across the nasal mucosa.

DETD . . . buffering agents can be selected such that when the formulation is delivered into the nasal cavity of a mammal, selected pH ranges are achieved therein upon contact with, e.g., a nasal mucosa. In the present invention, the pH of the compositions should be maintained from about 2.0 to about 6.0. It is desirable that the pH of the compositions is one which does not cause significant irritation to the nasal mucosa of a recipient upon administration.

DETD . . . laxative. The kit 10 also contains a methylnaltrexone capsule 14 containing methylnaltrexone pellets, some of which are enterically coated with pH sensitive material and some of which are constructed and arranged to release the methylnaltrexone immediately in the stomach. The kit. . .

DETD . . . preparation is optional. The diluent vial contains a diluent such as physiological saline for diluting what could be a concentrated solution or lyophilized powder of methylnaltrexone. The instructions can include instructions for mixing a particular amount of the diluent with a. . .

DETD [0107]

mg per tablet

Ingredients used (Trade name)	
Methylnaltrexone	75
Microcrystalline cellulose (Avicel PH 101)	13.30
Polyvinylpyrrolidone (Povidone K30)	3.5
Croscarmellose sodium (Ac-Di-Sol SD-711)	8
Dibasic Calcium Phosphate (Emcompress)	199
Microcrystalline cellulose (Avicel PH 200)	49.7
Magnesium Stearate (Hyqual)	1.7
Opadry II Clear	7.00
Water	as needed
Equipment used	
Key KG-5 Granulator	to make granules. . .

DETD [0110] 3. Granulate the above mixture using a solution of Povidone in water.

DETD [0118] 11. Coat the tablets with a solution of Opadry II Clear in water using a O'Hara Labcoat.

DETD [0127] 3. Granulate the above mixture using a solution of polyvinylpyrrolidone in water (10 g in 100 ml).

IT 57-27-2, Morphine, biological studies 577-11-7, Docusate sodium 33522-95-1D, Noroxymorphone, quaternized 73232-52-7, Methylnaltrexone
(combination therapy for constipation comprising laxative and peripheral opioid antagonist)

L9 ANSWER 15 OF 15 USPATFULL on STN

ACCESSION NUMBER: 2004:208951 USPATFULL
TITLE: Oral drug delivery system
INVENTOR(S): Yum, Su Il, Los Altos, CA, UNITED STATES
Schoenhard, Grant, San Carlos, CA, UNITED STATES
Tipton, Arthur J., Birmingham, AL, UNITED STATES
Gibson, John W., Springville, AL, UNITED STATES
Middleton, John C., Fort Collins, CO, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20040161382	A1	20040819
APPLICATION INFO.:	US 2003-737144	A1	20031215 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-433116P	20021213 (60)
	US 2003-517464P	20031104 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: JOHN S. PRATT, ESQ, KILPATRICK STOCKTON, LLP, 1100 PEACHTREE STREET, SUITE 2800, ATLANTA, GA, 30309

NUMBER OF CLAIMS: 79
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Page(s)
LINE COUNT: 1541
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . drug. Addicts also grind the tablet to extract the drug into alcohol or water to make a concentrated injectable drug solution . Administration of various abused drugs in this way produces a sudden high dose of drug into the blood stream making. . .

DETD [0043] Placebo refers to formulations without active drug (e.g., "a placebo solution" in Table 1).

DETD . . . gallate and/or reducing agents. Other examples include ascorbic acid, vitamin E, sodium bisulfite, butylhydroxyl toluene, BHA, acetylcysteine, monothioglycerol, phenyl-alpha-nathylamine, lecithin, EDTA.

DETD . . . E and cod-liver oil. Gelatin capsules are stable in storage, but once in the acid environment of the stomach (low pH less than about pH 4-5), the gelcap dissolves over a 10-15 minute period. In certain embodiments, the drug delivery device further comprises at least. . .

DETD . . . the viscosity of approximately 2 million centipoise (cP) at room temperature and approximately 600 cP at 80C. SAIB has unique solution-viscosity relationship in that the SAIB solutions in a number of organic solvents is significantly lower than these viscosity values for. . .

DETD . . . a beaker; while stirring slowly CAB and IPM were added (stir bar on stir plate); allowed to go completely into solution (stir bar on stir plate)--resulting mixture was left at 37° C. for 3 days; hot (80° C.) SAIB (shake in. . .

DETD . . . after immersion in 37° C. water for 6 hours (the column marked "placebo -H2O" refers to the viscosity of the solution before immersion in water, and the column marked "placebo +H2O" refers to the viscosity of the solution following immersion in water). The conditions of 37° C. and water immersion were intended to simulate in vivo conditions.

DETD . . . will increase with increasing CAB while the viscosity will decrease with increasing EL and IPM. Based on the theories of solution rheology, this was expected.

DETD Measurement of Drug Dissolution Rates in Low pH Solution (FIG. 7)

DETD . . . mechanism (as defined by United States Pharmacopia Apparatus II; VK 7000 USP II Dissolution Tester). 900 ml of 0.1N HCL solution at 37° C. was placed in the beaker and the solution was stirred at 50 rpm for 2 hours. During this period, the gelcap dissolved and the SAIB drug formulation was exposed to the low pH solution, and oxycodone dissolution begins. A number of 1 ml samples were taken and oxycodone concentration determined by HPLC (Perkin Elmer. . . Diode Array Detector 235C, or equivalent). Following the initial dissolution step, the content of the beaker was modified to adjust pH from 1 to 6.8 by adding sodium phosphate buffer. Temperature was maintained at 37° C., and dissolution of drug continued. . .

DETD . . . and CAB 381-20. As can be seen, the weight percent of drug that was extracted by the above described alcoholic solution decreased with increasing CAB 381-20 (see formulations 256-62-02, 256-62-04, 256-62-06 and 256-62-08). However, it was not obvious that

the addition. . . wt. % as in formulation 256-62-12, addition of 3 wt. % of IPM increased significantly the drug extractability by alcohol solution versus the formulations that did not contain IPM such as formulation 256-62-04. It was concluded therefore, that low drug extractability. . .

DETD . . . discovered unexpectedly that increasing contents of ethyl lactate, isopropyl myristate and CAB in concert reduced the drug extractability by alcoholic solution. From this experiment, it was discovered that IPM and CAB were quantitatively reciprocally interchangeable, such that increasing one component and. . . increasing IPM would have the same effect as increasing CAB. FIG. 3 shows cumulative percentage of drug extracted by alcoholic solution from various SAIB formulations vs. time (mins) for 4 formulations. Each formulation contains 12 mg/ml oxycodone. These formulations had IPM. . .

DETD . . . drug abuser may crush and grind an oxycodone tablet and dissolve it in water to extract the drug into aqueous solution for injecting. In the present experiment, the experimental dosage form was a SAIB-oxycodone gelcap with a formulation of SAIB:EL:IPM:CAB at. . . Oxycontin® tablet. Each dosage form was crushed with a mortar and pestle and ground in 5 ml water. The resulting solution /suspension was then filtered through a 0.45 micron filter into a flask and diluted to 50 ml with water. Oxycodone concentration. . .

DETD . . . mechanically crush a drug formulation so as to produce a powder which then can be inhaled or dissolved in a solution for injection. An experiment was performed to determine the characteristics of the current formulation, specifically with regard to lowering the. . .

DETD . . . It was discovered that optimum SAIB formulations, which manifest desirable pharmacokinetic profiles, must possess the following viscosity characteristics: the SAIB solution viscosity at 37° C. should be in the range from 1,000-30,000 cP. Further more the SAIB formulations following immersion in 37° C. water or aqueous buffer (pH 1-10) for 4-5 hours should optimally have the viscosity at 37° C. ranging from 3,000-50,000 cP.

IT 51-64-9, Dextroamphetamine 57-27-2, Morphine, biological studies 57-42-1, Meperidine 58-00-4, Apomorphine 59-02-9, α-Tocopherol 62-67-9, Nalorphine 64-17-5, Ethyl alcohol, biological studies 64-39-1, Promedol 67-63-0, Isopropyl alcohol, biological studies 67-68-5, DMSO, biological studies 76-41-5, Oxymorphone 76-57-3, Codeine 76-58-4, Ethylmorphine 76-99-3, Methadone 77-07-6, Levorphanol 77-14-5, Propheptazine 77-15-6, Ethoheptazine 77-20-3, Alphaprodine 77-93-0, Triethyl citrate 84-66-2, Diethyl phthalate 100-51-6, Benzyl alcohol, biological studies 102-76-1, Triacetine 108-32-7, Propylene carbonate 110-27-0, Isopropyl myristate 111-62-6, Ethyl oleate 113-45-1, Methylphenidate 120-51-4, Benzyl benzoate 125-28-0, Dihydrocodeine 125-29-1, Hydrocodone 126-13-6, Sucrose acetate isobutyrate 127-35-5, Phenazocine 131-11-3, Dimethyl phthalate 131-28-2, Narceine 143-52-2, Metopon 144-14-9, Anileridine 152-02-3, Levallorphan 302-41-0, Piritramide 357-56-2, Dextromoramide 359-83-1, Pentazocine 427-00-9, Desomorphine 428-37-5, Profadol 437-38-7, Fentanyl 441-61-2, Ethylmethylthiambutene 465-65-6, Naloxone 466-40-0, Isomethadone 466-97-7, Normorphine 466-99-9, Hydromorphone 467-18-5, Myrophine 467-83-4, Dipipanone 467-84-5, Phenadoxone 467-85-6, Normethadone 468-07-5, Phenomorphan 468-56-4, Hydroxypethidine 469-62-5,

Propoxyphene 469-79-4, Ketobemidone 509-60-4, Dihydromorphine 509-67-1, Pholcodine 509-78-4, Dimenoxadol 524-84-5, Dimethylthiambutene 545-90-4, Dimepheptanol 552-25-0, Diampromide 561-27-3, Heroin 561-48-8, Norpipanone 561-76-2, Properidine 562-26-5, Phenoperidine 639-48-5, Nicomorphine 641-36-1, Apocodeine 872-50-4, NMP, biological studies 911-65-9, Etonitazene 1531-12-0, Norlevorphanol 3194-25-0, Nalorphine dinicotinate 3572-80-3, Cyclazocine 3734-52-9, Metazocine 3861-76-5, Clonitazene 4163-15-9, Cyclorphan 4406-22-8, Cyprenorphine 9004-36-8, Cellulose acetate butyrate 10061-32-2, Levophenacylmorphan 13495-09-5, Piminodine 14297-87-1, Benzylmorphine 14357-78-9, Diprenorphine 14521-96-1, Etorphine 15301-48-1, Bezitramide 15686-91-6, Propiram 16590-41-3, Naltrexone 16676-26-9, Nalmexone 20594-83-6, Nalbuphine 25322-68-3, PEG 400 25384-17-2, Allylprodine 27203-92-5, Tramadol 31692-85-0, Glycofurol 36292-66-7, Ethylketocyclazocine 42408-82-2, Butorphanol 51931-66-9, Tilidine 52485-79-7, Buprenorphine 53648-55-8, Dezocine 54340-58-8, Meptazinol 55096-26-9, Nalmefene 56030-54-7, Sufentanil 56649-76-4, MR2266 58569-55-4, Metenkephalin 58822-25-6, Leuenkephalin 60617-12-1, β-Endorphin 61380-40-3, Lofentanil 67198-13-4 69671-17-6, α-Neoendorphin 71195-58-9, Alfentanil 72522-13-5, Eptazocine 72782-05-9, β-Funaltrexamine 73232-52-7, Methylnaltrexone 75644-90-5 75684-07-0, Bremazocine 78123-71-4, DAMGO 78995-14-9, Ohmefentanyl 82824-01-9, Naloxonazine 82970-70-5 85006-82-2, Dynorphin B 87151-85-7, Spiradoline 88161-22-2, Dynorphin A 88373-73-3 89352-67-0 93302-47-7, Naloxone methiodide 96744-75-1 103429-31-8, CTOP 105618-26-6, Norbinaltorphimine 111555-53-4, Naltrindole 111555-58-9, Naltriben 118111-54-9, Cyprodime 119630-94-3, Naloxone benzoylhydrazone 126876-64-0 132875-61-7, Remifentanyl 149997-88-6, (D-Ala2,Glu4)deltorphin 153611-34-8, BNTX
(oral delivery systems forming network within formulation and outer surface for desirable drug release kinetics)